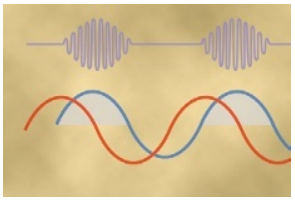
CHAPTER 41

Regulation of Respiration



The nervous system normally adjusts the rate of alveolar ventilation almost exactly to the demands of the body so that the oxygen pressure (P_{O_2}) and carbon dioxide pressure (P_{CO_2}) in the arterial blood are hardly altered, even during heavy exercise and most other types of respiratory stress. This chapter describes the function of this neurogenic system for regulation of respiration.

Respiratory Center

The *respiratory center* is composed of several groups of neurons located *bilaterally* in the *medulla oblongata* and pons of the brain stem, as shown in Figure 41-1. It is divided into three major collections of neurons: (1) a *dorsal respiratory group*, located in the dorsal portion of the medulla, which mainly causes inspiration; (2) a *ventral respiratory group*, located in the ventrolateral part of the medulla, which mainly causes expiration; and (3) the *pneumotaxic center*, located dorsally in the superior portion of the pons, which mainly controls rate and depth of breathing.

Dorsal Respiratory Group of Neurons—Its Control of Inspiration and of Respiratory Rhythm

The dorsal respiratory group of neurons plays the most fundamental role in the control of respiration and extends most of the length of the medulla. Most of its neurons are located within the *nucleus of the tractus solitarius (NTS)*, although additional neurons in the adjacent reticular substance of the medulla also play important roles in respiratory control. The NTS is the sensory termination of both the vagal and the glossopharyngeal nerves, which transmit sensory signals into the respiratory center from (1) peripheral chemoreceptors, (2) baroreceptors, and (3) several types of receptors in the lungs.

Rhythmical Inspiratory Discharges from the Dorsal Respiratory Group. The basic rhythm of respiration is generated mainly in the dorsal respiratory group of neurons. Even when all the peripheral nerves entering the medulla have been sectioned and the brain stem transected both above and below the medulla, this group of neurons still emits repetitive bursts of *inspiratory neuronal action potentials*. The basic cause of these repetitive discharges is unknown. In primitive animals, neural networks have been found in which activity of one set of neurons excites a second set, which in turn inhibits the first. Then, after a period of time, the mechanism repeats itself, continuing throughout the life of the animal. Therefore, most respiratory physiologists believe that some similar network of neurons is present in the human being, located entirely within the medulla; it probably involves not only the dorsal respiratory group but adjacent areas of the medulla as well, and it is responsible for the basic rhythm of respiration.

Inspiratory "Ramp" Signal. The nervous signal that is transmitted to the inspiratory muscles, mainly the diaphragm, is not an instantaneous burst of action potentials. Instead, it begins weakly and increases steadily in a ramp manner for about 2 seconds in normal respiration. Then it ceases abruptly for approximately the next 3 seconds, which turns off the excitation of the diaphragm and allows elastic recoil of the lungs and the chest wall to cause expiration. Next, the inspiratory signal begins again for another cycle; this cycle repeats again and again, with expiration occurring in between. Thus, the inspiratory signal is a *ramp signal*. The obvious advantage of the ramp is that it causes a steady increase in the volume of the lungs during inspiration, rather than inspiratory gasps.

There are two qualities of the inspiratory ramp that are controlled, as follows:

1. Control of the *rate of increase of the ramp signal* so that during heavy respiration, the ramp increases rapidly and therefore fills the lungs rapidly.
2. Control of the *limiting point at which the ramp suddenly ceases*. This is the usual method for controlling the rate of respiration; that is, the earlier the ramp ceases, the

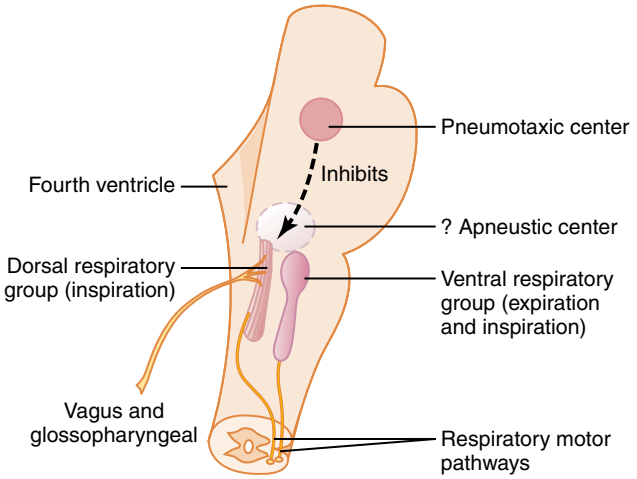


Figure 41-1 Organization of the respiratory center.

shorter the duration of inspiration. This also shortens the duration of expiration. Thus, the frequency of respiration is increased.

A Pneumotaxic Center Limits the Duration of Inspiration and Increases the Respiratory Rate

A *pneumotaxic center*, located dorsally in the *nucleus parabrachialis* of the upper pons, transmits signals to the inspiratory area. The primary effect of this center is to control the "switch-off" point of the inspiratory ramp, thus controlling the duration of the filling phase of the lung cycle. When the pneumotaxic signal is strong, inspiration might last for as little as 0.5 second, thus filling the lungs only slightly; when the pneumotaxic signal is weak, inspiration might continue for 5 or more seconds, thus filling the lungs with a great excess of air.

The function of the pneumotaxic center is primarily to limit inspiration. This has a secondary effect of increasing the rate of breathing because limitation of inspiration also shortens expiration and the entire period of each respiration. A strong pneumotaxic signal can increase the rate of breathing to 30 to 40 breaths per minute, whereas a weak pneumotaxic signal may reduce the rate to only 3 to 5 breaths per minute.

Ventral Respiratory Group of Neurons—Functions in Both Inspiration and Expiration

Located in each side of the medulla, about 5 millimeters anterior and lateral to the dorsal respiratory group of neurons, is the *ventral respiratory group of neurons*, found in the *nucleus ambiguus* rostrally and the *nucleus retroambiguus* caudally. The function of this neuronal group differs from that of the dorsal respiratory group in several important ways:

1. The neurons of the ventral respiratory group remain almost totally *inactive* during normal quiet respiration. Therefore, normal quiet breathing is caused only by repetitive inspiratory signals from the dorsal respiratory group transmitted mainly to the diaphragm, and expiration results from elastic recoil of the lungs and thoracic cage.
2. The ventral respiratory neurons do not appear to participate in the basic rhythmical oscillation that controls respiration.
3. When the respiratory drive for increased pulmonary ventilation becomes greater than normal, respiratory signals spill over into the ventral respiratory neurons from the basic oscillating mechanism of the dorsal respiratory area. As a consequence, the ventral respiratory area contributes extra respiratory drive as well.
4. Electrical stimulation of a few of the neurons in the ventral group causes inspiration, whereas stimulation of others causes expiration. Therefore, these neurons contribute to both inspiration and expiration. They are especially important in providing the powerful expiratory signals to the abdominal muscles during very heavy expiration. Thus, this area operates more or less as an overdrive mechanism when high levels of pulmonary ventilation are required, especially during heavy exercise.

Lung Inflation Signals Limit Inspiration—The Hering-Breuer Inflation Reflex

In addition to the central nervous system respiratory control mechanisms operating entirely within the brain stem, sensory nerve signals from the lungs also help control respiration. Most important, located in the muscular portions of the walls of the bronchi and bronchioles throughout the lungs are *stretch receptors* that transmit signals through the *vagi* into the dorsal respiratory group of neurons when the lungs become overstretched. These signals affect inspiration in much the same way as signals from the pneumotaxic center; that is, when the lungs become overly inflated, the stretch receptors activate an appropriate feedback response that "switches off" the inspiratory ramp and thus stops further inspiration. This is called the *Hering-Breuer inflation reflex*. This reflex also increases the rate of respiration, as is true for signals from the pneumotaxic center.

In humans, the Hering-Breuer reflex probably is not activated until the tidal volume increases to more than three times normal (>≈ 1.5 liters per breath). Therefore, this reflex appears to be mainly a protective mechanism for preventing excess lung inflation rather than an important ingredient in normal control of ventilation.

Control of Overall Respiratory Center Activity

Up to this point, we have discussed the basic mechanisms for causing inspiration and expiration, but it is also important to know how the intensity of the respiratory control signals is increased or decreased to match the ventilatory needs of the body. For example, during heavy exercise, the rates of oxygen usage and carbon dioxide formation are often increased to as much as 20 times normal, requiring

commensurate increases in pulmonary ventilation. The major purpose of the remainder of this chapter is to discuss this control of ventilation in accord with the respiratory needs of the body.

Chemical Control of Respiration

The ultimate goal of respiration is to maintain proper concentrations of oxygen, carbon dioxide, and hydrogen ions in the tissues. It is fortunate, therefore, that respiratory activity is highly responsive to changes in each of these.

Excess carbon dioxide or excess hydrogen ions in the blood mainly act directly on the respiratory center itself, causing greatly increased strength of both the inspiratory and the expiratory motor signals to the respiratory muscles.

Oxygen, in contrast, does not have a significant *direct* effect on the respiratory center of the brain in controlling respiration. Instead, it acts almost entirely on peripheral *chemoreceptors* located in the *carotid* and *aortic bodies*, and these in turn transmit appropriate nervous signals to the respiratory center for control of respiration.

Direct Chemical Control of Respiratory Center Activity by Carbon Dioxide and Hydrogen Ions

Chemosensitive Area of the Respiratory Center. We have discussed mainly three areas of the respiratory center: the dorsal respiratory group of neurons, the ventral respiratory group, and the pneumotaxic center. It is believed that none of these is affected directly by changes in blood carbon dioxide concentration or hydrogen ion concentration. Instead, an additional neuronal area, a *chemosensitive area*, shown in Figure 41-2, is located bilaterally, lying only 0.2 millimeter beneath the ventral surface of the medulla. This area is highly sensitive to changes in either blood P_{CO_2} or hydrogen ion concentration, and it in turn excites the other portions of the respiratory center.

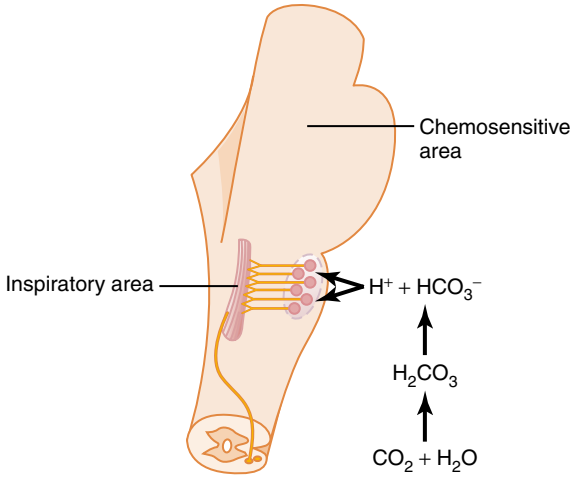


Figure 41-2 Stimulation of the *brain stem inspiratory* area by signals from the ***chemosensitive area*** located bilaterally in the medulla, lying only a fraction of a millimeter beneath the ventral medullary surface. Note also that hydrogen ions stimulate the chemosensitive area, but carbon dioxide in the fluid gives rise to most of the hydrogen ions.

Excitation of the Chemosensitive Neurons by Hydrogen Ions Is Likely the Primary Stimulus

The sensor neurons in the chemosensitive area are especially excited by hydrogen ions; in fact, it is believed that hydrogen ions may be the only important direct stimulus for these neurons. However, hydrogen ions do not easily cross the blood-brain barrier. For this reason, changes in hydrogen ion concentration in the blood have considerably less effect in stimulating the chemosensitive neurons than do changes in blood carbon dioxide, even though carbon dioxide is believed to stimulate these neurons secondarily by changing the hydrogen ion concentration, as explained in the following section.

Carbon Dioxide Stimulates the Chemosensitive Area

Although carbon dioxide has little direct effect in stimulating the neurons in the chemosensitive area, it does have a potent indirect effect. It does this by reacting with the water of the tissues to form carbonic acid, which dissociates into hydrogen and bicarbonate ions; the hydrogen ions then have a potent direct stimulatory effect on respiration. These reactions are shown in Figure 41-2.

Why does blood carbon dioxide have a more potent effect in stimulating the chemosensitive neurons than do blood hydrogen ions? The answer is that the blood-brain barrier is not very permeable to hydrogen ions, but carbon dioxide passes through this barrier almost as if the barrier did not exist. Consequently, whenever the blood P_{CO_2} increases, so does the P_{CO_2} of both the interstitial fluid of the medulla and the cerebrospinal fluid. In both these fluids, the carbon dioxide immediately reacts with the water to form new hydrogen ions. Thus, paradoxically, more hydrogen ions are released into the respiratory chemosensitive sensory area of the medulla when the blood carbon dioxide concentration increases than when the blood hydrogen ion concentration increases. For this reason, respiratory center activity is increased very strongly by changes in blood carbon dioxide, a fact that we subsequently discuss quantitatively.

Decreased Stimulatory Effect of Carbon Dioxide After the First 1 to 2 Days. Excitation of the respiratory center by carbon dioxide is great the first few hours after the blood carbon dioxide first increases, but then it gradually declines over the next 1 to 2 days, decreasing to about one-fifth the initial effect. Part of this decline results from renal readjustment of the hydrogen ion concentration in the circulating blood back toward normal after the carbon dioxide first increases the hydrogen concentration. The kidneys achieve this by increasing the blood bicarbonate, which binds with the hydrogen ions in the blood and cerebrospinal fluid to reduce their concentrations. But even more important, over a period of hours, the bicarbonate ions also slowly diffuse through the blood-brain and blood-cerebrospinal fluid barriers and combine directly

with the hydrogen ions adjacent to the respiratory neurons as well, thus reducing the hydrogen ions back to near normal. A change in blood carbon dioxide concentration therefore has a potent *acute* effect on controlling respiratory drive but only a weak *chronic* effect after a few days' adaptation.

Quantitative Effects of Blood PCO_2 and Hydrogen Ion Concentration on Alveolar Ventilation

Figure 41-3 shows quantitatively the approximate effects of blood P_{CO_2} and blood pH (which is an inverse logarithmic measure of hydrogen ion concentration) on alveolar ventilation. Note especially the very marked increase in ventilation caused by an increase in P_{CO_2} *in the normal range* between 35 and 75 mm Hg. This demonstrates the tremendous effect that carbon dioxide changes have in controlling respiration. By contrast, the change in respiration in the normal blood pH range between 7.3 and 7.5 is less than one-tenth as great.

Changes in Oxygen Have Little Direct Effect on Control of the Respiratory Center

Changes in oxygen concentration have virtually no *direct* effect on the respiratory center itself to alter respiratory drive (although oxygen changes do have an indirect effect, acting through the peripheral chemoreceptors, as explained in the next section).

We learned in Chapter 40 that the hemoglobin-oxygen buffer system delivers almost exactly normal amounts of oxygen to the tissues even when the pulmonary P_{O_2} changes from a value as low as 60 mm Hg up to a value as high as 1000 mm Hg. Therefore, except under special conditions, adequate delivery of oxygen can occur despite changes in lung ventilation ranging from slightly below one-half normal to as high as 20 or more times normal. This is not true for carbon dioxide because both the blood and tissue P_{CO_2} change inversely with the rate of pulmonary ventilation; thus, the processes of animal evolution have made carbon dioxide the major controller of respiration, not oxygen.

Yet for those special conditions in which the tissues get into trouble for lack of oxygen, the body has a special mechanism for respiratory control located in the peripheral chemoreceptors, outside the brain respiratory center; this mechanism responds when the blood oxygen falls too low, mainly below a P_{O_2} of 70 mm Hg, as explained in the next section.

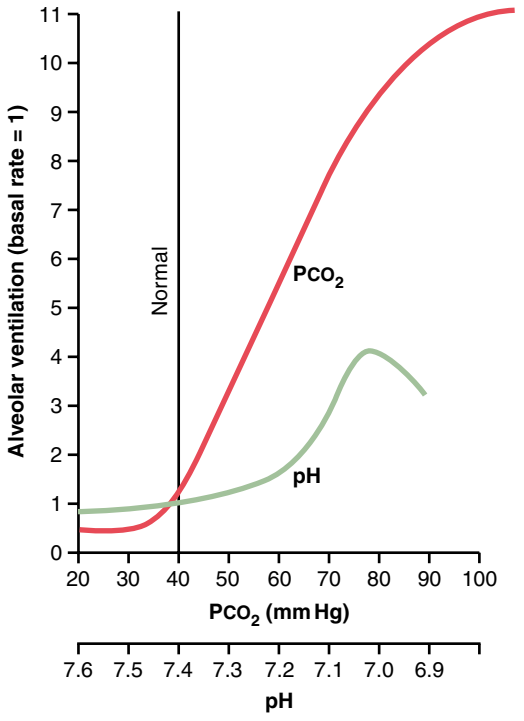


Figure 41-3 Effects of increased arterial blood P_{CO_2} and decreased arterial pH (increased hydrogen ion concentration) on the rate of alveolar ventilation.

Peripheral Chemoreceptor System for Control of Respiratory Activity—Role of Oxygen in Respiratory Control

In addition to control of respiratory activity by the respiratory center itself, still another mechanism is available for controlling respiration. This is the *peripheral chemoreceptor system*, shown in Figure 41-4. Special nervous chemical receptors, called *chemoreceptors*, are located in several areas outside the brain. They are especially important for detecting changes in oxygen in the blood, although they also respond to a lesser extent to changes in carbon dioxide and hydrogen ion concentrations. The chemoreceptors transmit nervous signals to the respiratory center in the brain to help regulate respiratory activity.

Most of the chemoreceptors are in the *carotid bodies*. However, a few are also in the *aortic bodies*, shown in the lower part of Figure 41-4, and a very few are located elsewhere in association with other arteries of the thoracic and abdominal regions.

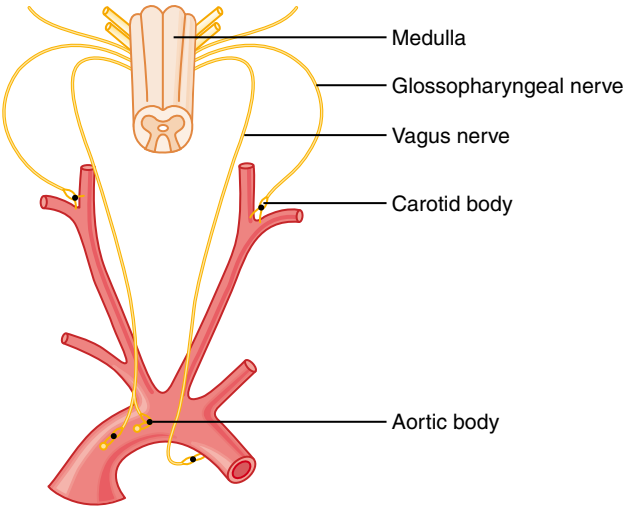


Figure 41-4 Respiratory control by peripheral chemoreceptors in the carotid and aortic bodies.

The *carotid bodies* are located bilaterally in the bifurcations of the common carotid arteries. Their afferent nerve fibers pass through Hering's nerves to the *glossopharyngeal nerves* and then to the dorsal respiratory area of the medulla. The *aortic bodies* are located along the arch of the aorta; their afferent nerve fibers pass through the *vagi*, also to the dorsal medullary respiratory area.

Each of the chemoreceptor bodies receives its own special blood supply through a minute artery directly from the adjacent arterial trunk. Further, blood flow through these bodies is extreme, 20 times the weight of the bodies themselves each minute. Therefore, the percentage of oxygen removed from the flowing blood is virtually zero. This means that *the chemoreceptors are exposed at all times to arterial blood*, not venous blood, and their P_{O_2}s are arterial P_{O_2}s.

***Decreased* Arterial Oxygen Stimulates the Chemoreceptors.** When the oxygen concentration in the arterial blood falls below normal, the chemoreceptors become strongly stimulated. This is demonstrated in Figure 41-5, which shows the effect of different levels of *arterial* P_{O_2} on the rate of nerve impulse transmission from a carotid body. Note that the impulse rate is particularly sensitive to changes in arterial P_{O_2} in the range of 60 down to 30 mm Hg, a range in which hemoglobin saturation with oxygen decreases rapidly.

***Increased* Carbon Dioxide and Hydrogen Ion Concentration Stimulates the Chemoreceptors.** An increase in either carbon dioxide concentration or hydrogen ion concentration also excites the chemoreceptors and, in this way, indirectly increases respiratory activity. However, the direct effects of both these factors in the respiratory center itself are much more powerful than their effects mediated through the chemoreceptors (about seven times as powerful). Yet there is one difference between the peripheral and central effects of carbon dioxide: The stimulation by way of the peripheral chemoreceptors occurs as much as five times as rapidly as central stimulation, so the peripheral chemoreceptors might be especially important in increasing the rapidity of response to carbon dioxide at the onset of exercise.

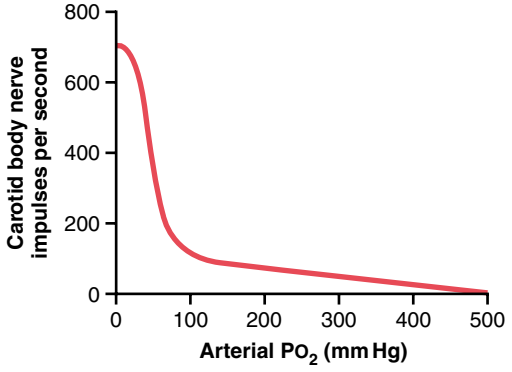


Figure 41-5 Effect of arterial P_{O_2} on impulse rate from the carotid body.

Basic Mechanism of Stimulation of the Chemoreceptors by Oxygen Deficiency. The exact means by which low P_{O_2} excites the nerve endings in the carotid and aortic bodies are still unknown. However, these bodies have multiple highly characteristic glandular-like cells, called *glomus cells*, which synapse directly or indirectly with the nerve endings. Some investigators have suggested that these glomus cells might function as the chemoreceptors and then stimulate the nerve endings. But other studies suggest that the nerve endings themselves are directly sensitive to the low P_{O_2}.

Effect of Low Arterial P_{O_2} to Stimulate Alveolar Ventilation When Arterial Carbon Dioxide and Hydrogen Ion Concentrations Remain Normal

Figure 41-6 shows the effect of low arterial P_{O_2} on alveolar ventilation when the P_{CO_2} and the hydrogen ion concentration are kept constant at their normal levels. In other words, in this figure, only the ventilatory drive, due to the effect of low oxygen on the chemoreceptors, is active. The figure shows almost no effect on ventilation as long as the arterial P_{O_2} remains greater than 100 mm Hg. But at pressures lower than 100 mm Hg, ventilation approximately doubles when the arterial P_{O_2} falls to 60 mm Hg and can increase as much as fivefold at very low P_{O_2}s. Under these conditions, low arterial P_{O_2} obviously drives the ventilatory process quite strongly.

Because the effect of hypoxia on ventilation is modest for P_{O_2}s greater than 60 to 80 mm Hg, the P_{CO_2} and the hydrogen ion response are mainly responsible for regulating ventilation in healthy humans at sea level.

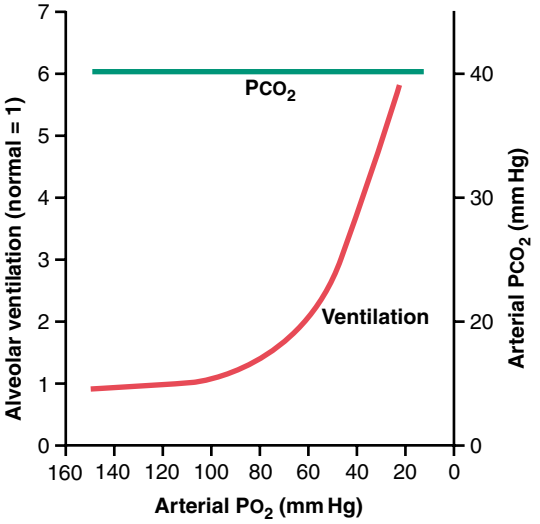


Figure 41-6 The lower curve demonstrates the effect of different levels of arterial P_{O_2} on alveolar ventilation, showing a sixfold increase in ventilation as the P_{O_2} decreases from the normal level of 100 mm Hg to 20 mm Hg. The upper line shows that the arterial P_{CO_2} was kept at a constant level during the measurements of this study; pH also was kept constant.

Chronic Breathing of Low Oxygen Stimulates Respiration Even More—The Phenomenon of "Acclimatization"

Mountain climbers have found that when they ascend a mountain slowly, over a period of days rather than a period of hours, they breathe much more deeply and therefore can withstand far lower atmospheric oxygen concentrations than when they ascend rapidly. This is called *acclimatization*.

The reason for acclimatization is that, within 2 to 3 days, the respiratory center in the brain stem loses about four fifths of its sensitivity to changes in P_{CO_2} and hydrogen ions. Therefore, the excess ventilatory blow-off of carbon dioxide that normally would inhibit an increase in respiration fails to occur, and low oxygen can drive the respiratory system to a much higher level of alveolar ventilation than under acute conditions. Instead of the 70 percent increase in ventilation that might occur after acute exposure to low oxygen, the alveolar ventilation often increases 400 to 500 percent after 2 to 3 days of low oxygen; this helps immensely in supplying additional oxygen to the mountain climber.

Composite Effects of P_{CO_2}, pH, and P_{O_2} on Alveolar Ventilation

Figure 41-7 gives a quick overview of the manner in which the chemical factors P_{O_2}, P_{CO_2}, and pH together affect alveolar ventilation. To understand this diagram, first observe the four red curves. These curves were recorded at different levels of arterial P_{O_2}—40 mm Hg, 50 mm Hg, 60 mm Hg, and 100 mm Hg. For each of these curves, the P_{CO_2} was changed from lower to higher levels. Thus, this "family" of red curves represents the combined effects of alveolar P_{CO_2} and P_{O_2} on ventilation.

Now observe the green curves. The red curves were measured at a blood pH of 7.4; the green curves were measured at a pH of 7.3. We now have two families of curves representing the combined effects of P_{CO_2} and P_{O_2} on ventilation at two different pH values. Still other families of curves would be displaced to the right at higher pHs and displaced to the left at lower pHs. Thus, using this diagram, one can predict the level of alveolar ventilation for most combinations of alveolar P_{CO_2}, alveolar P_{O_2}, and arterial pH.

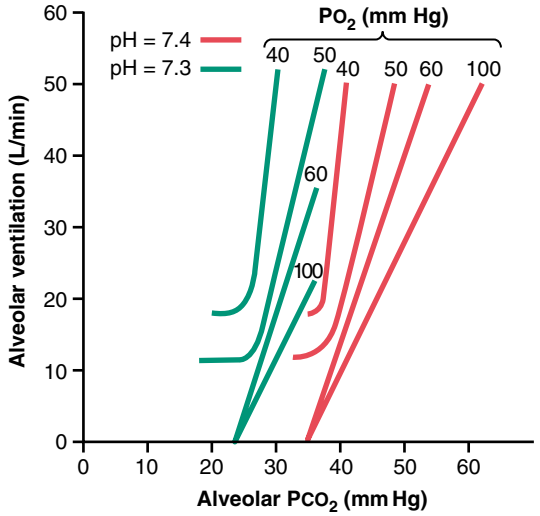


Figure 41-7 Composite diagram showing the interrelated effects of P_{CO_2}, P_{O_2}, and pH on alveolar ventilation. (Drawn from data in Cunningham DJC, Lloyd BB: The Regulation of Human Respiration. Oxford: Blackwell Scientific Publications, 1963.)

Regulation of Respiration During Exercise

In strenuous exercise, oxygen consumption and carbon dioxide formation can increase as much as 20-fold. Yet, as illustrated in Figure 41-8, in the healthy athlete, alveolar ventilation ordinarily increases almost exactly in step with the increased level of oxygen metabolism. The arterial P_{O_2}, P_{CO_2}, and pH remain *almost exactly normal*.

In trying to analyze what causes the increased ventilation during exercise, one is tempted to ascribe this to increases in blood carbon dioxide and hydrogen ions, plus a decrease in blood oxygen. However, this is questionable because measurements of arterial P_{CO_2}, pH, and P_{O_2} show that none of these values changes significantly during exercise, so none of them becomes abnormal enough to stimulate respiration so vigorously as observed during strenuous exercise. Therefore, the question must be asked: What causes intense ventilation during exercise? At least one effect seems to be predominant. The brain, on transmitting motor impulses to the exercising muscles, is believed to transmit at the same time collateral impulses into the brain stem to excite the respiratory center. This is analogous to the stimulation of the vasomotor center of the brain stem during exercise that causes a simultaneous increase in arterial pressure.

Actually, when a person begins to exercise, a large share of the total increase in ventilation begins immediately on initiation of the exercise, before any blood chemicals have had time to change. It is likely that most of the increase in respiration results from neurogenic signals transmitted directly into the brain stem respiratory center at the same time that signals go to the body muscles to cause muscle contraction.

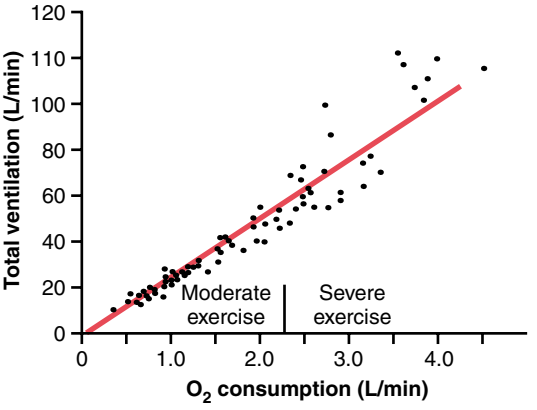


Figure 41-8 Effect of exercise on oxygen consumption and ventilatory rate. (From Gray JS: Pulmonary Ventilation and Its Physiological Regulation. Springfield, Ill: Charles C Thomas, 1950.)

Interrelation Between Chemical Factors and Nervous Factors in the Control of Respiration During Exercise. When a person exercises, direct nervous signals presumably stimulate the respiratory center *almost* the proper amount to supply the extra oxygen required for exercise and to blow off extra carbon dioxide. Occasionally, however, the nervous respiratory control signals are either too strong or too weak. Then chemical factors play a significant role in bringing about the final adjustment of respiration required to keep the oxygen, carbon dioxide, and hydrogen ion concentrations of the body fluids as nearly normal as possible.

This is demonstrated in Figure 41-9, which shows in the lower curve changes in alveolar ventilation during a 1-minute period of exercise and in the upper curve changes in arterial P_{CO_2}. Note that at the onset of exercise, the alveolar ventilation increases almost instantaneously, without an initial increase in arterial P_{CO_2}. In fact, this increase in ventilation is usually great enough so that at first it actually *decreases* arterial P_{CO_2} below normal, as shown in the figure. The presumed reason that the ventilation forges ahead of the buildup of blood carbon dioxide is that the brain provides an "anticipatory" stimulation of respiration at the onset of exercise, causing extra alveolar ventilation even before it is necessary. However, after about 30 to 40 seconds, the amount of carbon dioxide released into the blood from the active muscles approximately matches the increased rate of ventilation, and the arterial P_{CO_2} returns essentially to normal even as the exercise continues, as shown toward the end of the 1-minute period of exercise in the figure.

Figure 41-10 summarizes the control of respiration during exercise in still another way, this time more quantitatively. The lower curve of this figure shows the

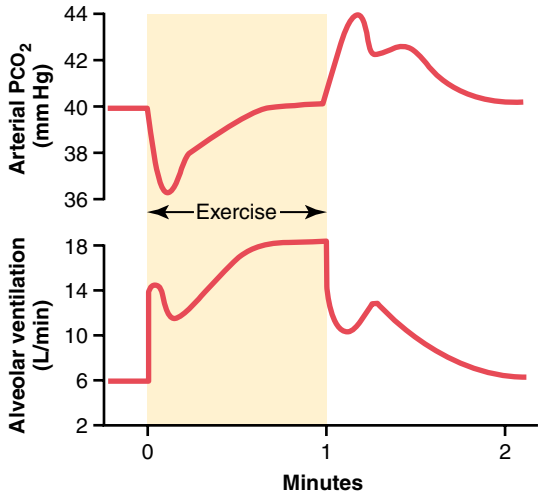


Figure 41-9 Changes in alveolar ventilation (*bottom curve*) and arterial PCO_2 (*top curve*) during a 1-minute period of exercise and also after termination of exercise. (Extrapolated to the human from data in dogs in Bainton CR: Effect of speed vs grade and shivering on ventilation in dogs during active exercise. J Appl Physiol 33:778, 1972.)

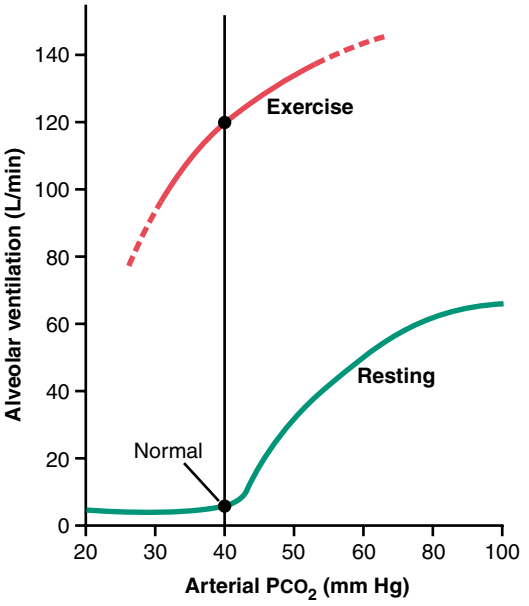


Figure 41-10 Approximate effect of maximum exercise in an athlete to shift the alveolar P_{CO_2}-ventilation response curve to a level much higher than normal. The shift, believed to be caused by neurogenic factors, is almost exactly the right amount to maintain arterial P_{CO_2} at the normal level of 40 mm Hg both in the resting state and during heavy exercise.

effect of different levels of arterial P_{CO_2} on alveolar ventilation when the body is at rest—that is, not exercising. The upper curve shows the approximate shift of this ventilatory curve caused by neurogenic drive from the respiratory center that occurs during heavy exercise. The points indicated on the two curves show the arterial P_{CO_2} first in the resting state and then in the exercising state. Note in both instances that the P_{CO_2} is at the normal level of 40 mm Hg. In other words, the neurogenic factor shifts the curve about 20-fold in the upward direction, so ventilation almost matches the rate of carbon dioxide release, thus keeping arterial P_{CO_2} near its normal value. The upper curve of Figure 41-10 also shows that if, during exercise, the arterial P_{CO_2} does change from its normal value of 40 mm Hg, it has an extra stimulatory effect on ventilation at a P_{CO_2} greater than 40 mm Hg and a depressant effect at a P_{CO_2} less than 40 mm Hg.

Neurogenic Control of Ventilation During Exercise May Be Partly a Learned Response. Many experiments suggest that the brain's ability to shift the ventilatory response curve during exercise, as shown in Figure 41-10, is at least partly a *learned* response. That is, with repeated periods of exercise, the brain becomes progressively more able to provide the proper signals required to keep the blood P_{CO_2} at its normal level. Also, there is reason to believe that even the cerebral cortex is involved in this learning because experiments that block only the cortex also block the learned response.

Other Factors That Affect Respiration

Voluntary Control of Respiration. Thus far, we have discussed the involuntary system for the control of respiration. However, we all know that for short periods of time, respiration can be controlled voluntarily and that one can hyperventilate or hypoventilate to such an extent that serious derangements in P_{CO_2}, pH, and P_{O_2} can occur in the blood.

Effect of Irritant Receptors in the Airways. The epithelium of the trachea, bronchi, and bronchioles is supplied with sensory nerve endings called *pulmonary irritant receptors* that are stimulated by many incidents. These cause coughing and sneezing, as discussed in Chapter 39. They may also cause bronchial constriction in such diseases as asthma and emphysema.

Function of Lung "J Receptors". A few sensory nerve endings have been described in the alveolar walls in *juxtaposition* to the pulmonary capillaries—hence the name "J receptors." They are stimulated especially when the pulmonary capillaries become engorged with blood or when pulmonary edema occurs in such conditions as congestive heart failure. Although the functional role of the J receptors is not clear, their excitation may give the person a feeling of dyspnea.

Brain Edema Depresses the Respiratory Center. The activity of the respiratory center may be depressed or even inactivated by acute brain edema resulting from brain concussion. For instance, the head might be struck against some solid object, after which the damaged brain tissues swell, compressing the cerebral arteries against the cranial vault and thus partially blocking cerebral blood supply.

Occasionally, respiratory depression resulting from brain edema can be relieved temporarily by intravenous injection of hypertonic solutions such as highly concentrated mannitol solution. These solutions osmotically remove some of the fluids of the brain, thus relieving intracranial pressure and sometimes re-establishing respiration within a few minutes.

Anesthesia. Perhaps the most prevalent cause of respiratory depression and respiratory arrest is overdosage with anesthetics or narcotics. For instance, sodium pentobarbital depresses the respiratory center considerably more than many other anesthetics, such as halothane. At one time, morphine was used as an anesthetic, but this drug is now used only as an adjunct to anesthetics because it greatly depresses the respiratory center while having less ability to anesthetize the cerebral cortex.

Periodic Breathing. An abnormality of respiration called *periodic breathing* occurs in a number of disease conditions. The person breathes deeply for a short interval and then breathes slightly or not at all for an additional interval, with the cycle repeating itself over and over. One type of periodic breathing, *Cheyne-Stokes breathing*, is characterized by slowly waxing and waning respiration occurring about every 40 to 60 seconds, as illustrated in Figure 41-11.

Basic Mechanism of Cheyne-Stokes Breathing. The basic cause of Cheyne-Stokes breathing is the following: When a person overbreathes, thus blowing off too much carbon dioxide from the pulmonary blood while at the same time increasing blood oxygen, it takes several seconds before the changed pulmonary blood can be transported to the brain and inhibit the excess ventilation. By this time, the person has already overventilated for an extra few seconds.

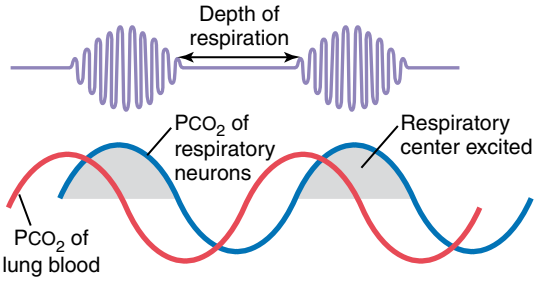


Figure 41-11 Cheyne-Stokes breathing, showing changing P_{CO_2} in the pulmonary blood (*red line*) and delayed changes in the P_{CO_2} of the fluids of the respiratory center (*blue line*).

Therefore, when the overventilated blood finally reaches the brain respiratory center, the center becomes depressed to an excessive amount. Then the opposite cycle begins. That is, carbon dioxide increases and oxygen decreases in the alveoli. Again, it takes a few seconds before the brain can respond to these new changes. When the brain does respond, the person breathes hard once again and the cycle repeats.

The basic cause of Cheyne-Stokes breathing occurs in everyone. However, under normal conditions, this mechanism is highly "damped." That is, the fluids of the blood and the respiratory center control areas have large amounts of dissolved and chemically bound carbon dioxide and oxygen. Therefore, normally, the lungs cannot build up enough extra carbon dioxide or depress the oxygen sufficiently in a few seconds to cause the next cycle of the periodic breathing. But under two separate conditions, the damping factors can be overridden and Cheyne-Stokes breathing does occur:

1. When a *long delay occurs for transport of blood from the lungs to the brain*, changes in carbon dioxide and oxygen in the alveoli can continue for many more seconds than usual. Under these conditions, the storage capacities of the alveoli and pulmonary blood for these gases are exceeded; then, after a few more seconds, the periodic respiratory drive becomes extreme and Cheyne-Stokes breathing begins. This type of Cheyne-Stokes breathing often occurs in patients with *severe cardiac failure* because blood flow is slow, thus delaying the transport of blood gases from the lungs to the brain. In fact, in patients with chronic heart failure, Cheyne-Stokes breathing can sometimes occur on and off for months.
2. A second cause of Cheyne-Stokes breathing is *increased negative feedback gain* in the respiratory control areas. This means that a change in blood carbon dioxide or oxygen causes a far greater change in ventilation than normally. For instance, instead of the normal 2- to 3-fold increase in ventilation that occurs when the P_{CO_2} rises 3 mm Hg, the same 3 mm Hg rise might increase ventilation 10- to 20-fold. The brain feedback tendency for periodic breathing is now strong enough to cause Cheyne-Stokes breathing without extra blood flow delay between the lungs and brain. This type of Cheyne-Stokes breathing occurs mainly in patients with *brain damage*. The brain damage often turns off the respiratory drive entirely for a few seconds; then an extra intense increase in blood carbon dioxide turns it back on with great force. Cheyne-Stokes breathing of this type is frequently a prelude to death from brain malfunction.

Typical records of changes in pulmonary and respiratory center P_{CO_2} during Cheyne-Stokes breathing are shown in Figure 41-11. Note that the P_{CO_2} of the pulmonary blood changes *in advance* of the P_{CO_2} of the respiratory neurons. But the depth of respiration corresponds with the P_{CO_2} in the brain, not with the P_{CO_2} in the pulmonary blood where the ventilation is occurring.

Sleep Apnea

The term *apnea* means absence of spontaneous breathing. Occasional apneas occur during normal sleep, but in persons with *sleep apnea*, the frequency and duration are greatly increased, with episodes of apnea lasting for 10 seconds or longer and occurring 300 to 500 times each night. Sleep apneas can be caused by obstruction of the upper airways, especially the pharynx, or by impaired central nervous system respiratory drive.

Obstructive Sleep Apnea Is Caused by Blockage of the Upper Airway. The muscles of the pharynx normally keep this passage open to allow air to flow into the lungs during inspiration. During sleep, these muscles usually relax, but the airway passage remains open enough to permit adequate airflow. Some individuals have an especially narrow passage, and relaxation of these muscles during sleep causes the pharynx to completely close so that air cannot flow into the lungs.

In persons with sleep apnea, loud *snoring* and *labored breathing* occur soon after falling asleep. The snoring proceeds, often becoming louder, and is then interrupted by a long silent period during which no breathing (apnea) occurs. These periods of apnea result in significant decreases in P_{O_2} and increases in P_{CO_2}, which greatly stimulate respiration. This, in turn, causes sudden attempts to breathe, which result in loud snorts and gasps followed by snoring and repeated episodes of apnea. The periods of apnea and labored breathing are repeated several hundred times during the night, resulting in fragmented, restless sleep. Therefore, patients with sleep apnea usually have excessive daytime *drowsiness*, as well as other disorders, including increased sympathetic activity, high heart rates, pulmonary and systemic hypertension, and a greatly elevated risk for cardiovascular disease.

Obstructive sleep apnea most commonly occurs in older, obese persons in whom there is increased fat deposition in the soft tissues of the pharynx or compression of the pharynx due to excessive fat masses in the neck. In a few individuals, sleep apnea may be associated with nasal obstruction, a very large tongue, enlarged tonsils, or certain shapes of the palate that greatly increase resistance to the flow of air to the lungs during inspiration. The most common treatments of obstructive sleep apnea include (1) surgery to remove excess fat tissue at the back of the throat (a procedure called *uvulopalatopharyngoplasty*), to remove enlarged tonsils or adenoids, or to create an opening in the trachea (tracheostomy) to bypass the obstructed airway during sleep, and (2) nasal ventilation with *continuous positive airway pressure* (CPAP).

"Central" Sleep Apnea Occurs When the Neural Drive to Respiratory Muscles Is Transiently Abolished. In a few persons with sleep apnea, the central nervous system drive to the ventilatory muscles transiently ceases. Disorders that can cause cessation of the ventilatory drive during sleep include *damage to the central respiratory centers or abnormalities of the respiratory neuromuscular apparatus*. Patients affected by central sleep apnea may have decreased ventilation when they are awake, although they are fully capable of normal voluntary breathing. During sleep, their breathing disorders usually worsen, resulting in more frequent episodes of apnea that decrease P_{O_2} and increase P_{CO_2} until a critical level is reached that eventually stimulates respiration. These transient instabilities of respiration cause restless sleep and clinical features similar to those observed in obstructive sleep apnea.

In most patients the cause of central sleep apnea is unknown, although instability of the respiratory drive can result from strokes or other disorders that make the respiratory centers of the brain less responsive to the stimulatory effects of carbon dioxide and hydrogen ions. Patients with this disease are extremely sensitive to even small doses of sedatives or narcotics, which further reduce the responsiveness of the respiratory centers to the stimulatory effects of carbon dioxide. Medications that stimulate the respiratory centers can sometimes be helpful, but ventilation with CPAP at night is usually necessary.

Bibliography

Albert R, Spiro S, Jett J: *Comprehensive Respiratory Medicine*, Philadelphia, 2002, Mosby.

Bradley TD, Floras JS: Obstructive sleep apnoea and its cardiovascular consequences, *Lancet* 373:82, 2009.

Datta A, Tipton M: Respiratory responses to cold water immersion: neural pathways, interactions, and clinical consequences awake and asleep, *J Appl Physiol* 100:2057, 2006.

Dean JB, Ballantyne D, Cardone DL, et al: Role of gap junctions in CO_2 chemoreception and respiratory control, *Am J Physiol Lung Cell Mol Physiol* 283:L665, 2002.

Dempsey JA, McKenzie DC, Haverkamp HC, et al: Update in the understanding of respiratory limitations to exercise performance in fit, active adults, *Chest* 134:613, 2008.

Eckert DJ, Jordan AS, Merchia P, et al: Central sleep apnea: Pathophysiology and treatment, *Chest* 131:595, 2007.

Forster HV: Plasticity in the control of breathing following sensory denervation, *J Appl Physiol* 94:784, 2003.

Gaultier C, Gallego J: Neural control of breathing: insights from genetic mouse models, *J Appl Physiol* 104:1522, 2008.

Gray PA: Transcription factors and the genetic organization of brain stem respiratory neurons, *J Appl Physiol* 104:1513, 2008.

Guyenet PG: The 2008 Carl Ludwig Lecture: retrotrapezoid nucleus, CO2 homeostasis, and breathing automaticity, *J Appl Physiol* 105:404, 2008.

Hilaire G, Pasaro R: Genesis and control of the respiratory rhythm in adult mammals, *News Physiol Sci* 18:23, 2003.

Horner RL, Bradley TD: Update in sleep and control of ventilation 2008, *Am J Respir Crit Care Med* 179:528, 2009.

Morris KF, Baekey DM, Nuding SC, et al: Neural network plasticity in respiratory control, *J Appl Physiol* 94:1242, 2003.

Somers VK, White DP, Amin R, et al: *J Am Coll Cardiol* 52:686, 2008.

Sharp FR, Bernaudin M: HIF1 and oxygen sensing in the brain, *Nat Rev Neurosci* 5:437, 2004.

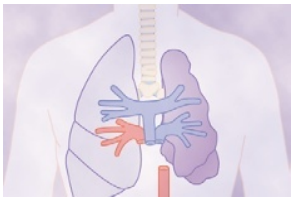
Thach BT: Some aspects of clinical relevance in the maturation of respiratory control in infants, *J Appl Physiol* 104:1828, 2008.

West JB: *Pulmonary Physiology-The Essentials*, Baltimore, 2003, Lippincott Williams & Wilkins.

Younes M: Role of respiratory control mechanisms in the pathogenesis of obstructive sleep disorders, *J Appl Physiol* 105:1389, 2008.

Young T, Skatrud J, Peppard PE: Risk factors for obstructive sleep apnea in adults, *JAMA* 291:2013, 2004.

Respiratory Insufficiency—Pathophysiology, Diagnosis, Oxygen Therapy



Diagnosis and treatment of most respiratory disorders depend heavily on understanding the basic physiologic principles of respiration and gas exchange. Some respiratory diseases result from inadequate ventilation. Others result from abnormalities of diffusion through the pulmonary membrane or abnormal blood transport of gases between the lungs and tissues. Therapy is often entirely different for these diseases, so it is no longer satisfactory simply to make a diagnosis of "respiratory insufficiency."

Useful Methods for Studying Respiratory Abnormalities

In the previous few chapters, we have discussed several methods for studying respiratory abnormalities, including measuring vital capacity, tidal air, functional residual capacity, dead space, physiologic shunt, and physiologic dead space. This array of measurements is only part of the armamentarium of the clinical pulmonary physiologist. Some other tools are described here.

Study of Blood Gases and Blood pH

Among the most fundamental of all tests of pulmonary performance are determinations of the blood P_{O_2}, CO_2, and pH. It is often important to make these measurements rapidly as an aid in determining appropriate therapy for acute respiratory distress or acute abnormalities of acid-base balance. Several simple and rapid methods have been developed to make these measurements within minutes, using no more than a few drops of blood. They are the following.

Determination of Blood pH. Blood pH is measured using a glass pH electrode of the type used in all chemical laboratories. However, the electrodes used for this purpose are miniaturized. The voltage generated by the glass electrode is a direct measure of pH, and this is generally read directly from a voltmeter scale, or it is recorded on a chart.

Determination of Blood CO_2. A glass electrode pH meter can also be used to determine blood CO_2 in the following way: When a weak solution of sodium bicarbonate is exposed to carbon dioxide gas, the carbon dioxide dissolves in the solution until an equilibrium state is established. In this equilibrium state, the pH of the solution is a function of the carbon dioxide and bicarbonate ion concentrations in accordance with the Henderson-Hasselbalch equation that is explained in Chapter 30; that is,

$$pH = 6.1 + \log \frac{HCO_3^-}{CO_2}$$

When the glass electrode is used to measure CO_2 in blood, a miniature glass electrode is surrounded by a thin plastic membrane. In the space between the electrode and plastic membrane is a solution of sodium bicarbonate of known concentration. Blood is then superfused onto the outer surface of the plastic membrane, allowing carbon dioxide to diffuse from the blood into the bicarbonate solution. Only a drop or so of blood is required. Next, the pH is measured by the glass electrode, and the CO_2 is calculated by use of the previously given formula.

Determination of Blood PO_2. The concentration of oxygen in a fluid can be measured by a technique called *polarography*. Electric current is made to flow between a small negative electrode and the solution. If the voltage of the electrode is more than −0.6 volt different from the voltage of the solution, oxygen will deposit on the electrode. Furthermore, the rate of current flow through the electrode will be directly proportional to the concentration of oxygen (and therefore to PO_2 as well). In practice, a negative platinum electrode with a surface area of about 1 square millimeter is used, and this is separated from the blood by a thin plastic membrane that allows diffusion of oxygen but not diffusion of proteins or other substances that will "poison" the electrode.

Often all three of the measuring devices for pH, CO_2, and P_{O_2} are built into the same apparatus, and all these

measurements can be made within a minute or so using a single, droplet-size sample of blood. Thus, changes in the blood gases and pH can be followed almost moment by moment at the bedside.

Measurement of Maximum Expiratory Flow

In many respiratory diseases, particularly in asthma, the resistance to airflow becomes especially great during expiration, sometimes causing tremendous difficulty in breathing. This has led to the concept called *maximum expiratory flow*, which can be defined as follows: When a person expires with great force, the expiratory airflow reaches a maximum flow beyond which the flow cannot be increased any more, even with greatly increased additional force. This is the maximum expiratory flow. The maximum expiratory flow is much greater when the lungs are filled with a large volume of air than when they are almost empty. These principles can be understood by referring to Figure 42-1.

Figure 42-1*A* shows the effect of increased pressure applied to the outsides of the alveoli and air passageways caused by compressing the chest cage. The arrows indicate that the same pressure compresses the outsides of both the alveoli and the bronchioles. Therefore, not only does this pressure force air from the alveoli toward the bronchioles, but it also tends to collapse the bronchioles at the same time, which will oppose movement of air to the exterior. Once the bronchioles have almost completely collapsed, further expiratory force can still greatly increase the alveolar pressure, but it also increases the degree of bronchiolar collapse and airway resistance by an equal amount, thus preventing further increase in flow.

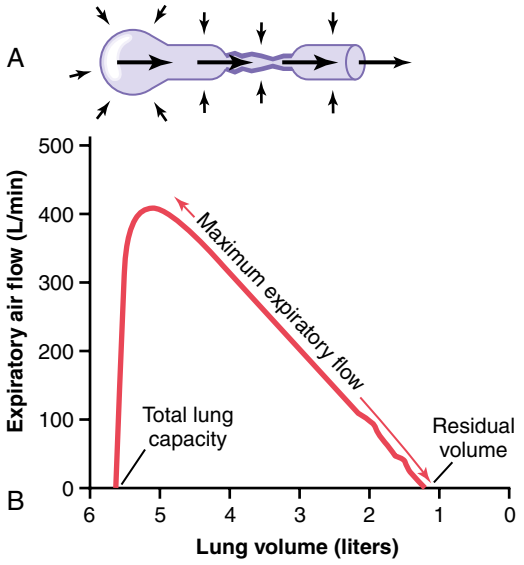


Figure 42-1 *A*, Collapse of the respiratory passageway during maximum expiratory effort, an effect that limits expiratory flow rate. *B*, Effect of lung volume on the maximum expiratory air flow, showing decreasing maximum expiratory air flow as the lung volume becomes smaller.

Therefore, beyond a critical degree of expiratory force, a maximum expiratory flow has been reached.

Figure 42-1*B* shows the effect of different degrees of lung collapse (and therefore of bronchiolar collapse as well) on the maximum expiratory flow. The curve recorded in this section shows the maximum expiratory flow at all levels of lung volume after a healthy person first inhales as much air as possible and then expires with maximum expiratory effort until he or she can expire at no greater rate. Note that the person quickly reaches a *maximum expiratory airflow* of more than 400 L/min. But regardless of how much additional expiratory effort the person exerts, this is still the maximum flow rate that he or she can achieve.

Note also that as the lung volume becomes smaller, the maximum expiratory flow rate also becomes less. The main reason for this is that in the enlarged lung the bronchi and bronchioles are held open partially by way of elastic pull on their outsides by lung structural elements; however, as the lung becomes smaller, these structures are relaxed so that the bronchi and bronchioles are collapsed more easily by external chest pressure, thus progressively reducing the maximum expiratory flow rate as well.

Abnormalities of the Maximum Expiratory Flow-Volume Curve. Figure 42-2 shows the normal maximum expiratory flow-volume curve, along with two additional flow-volume curves recorded in two types of lung diseases: constricted lungs and partial airway obstruction. Note that the *constricted lungs* have both reduced total lung capacity (TLC) and reduced residual volume (RV). Furthermore, because the lung cannot expand to a normal maximum volume, even with the greatest possible expiratory effort, the maximal expiratory flow cannot rise to equal that of the normal curve. Constricted lung diseases include fibrotic diseases of the lung itself, such as *tuberculosis* and *silicosis*, and diseases that constrict the chest cage, such as *kyphosis, scoliosis*, and *fibrotic pleurisy*.

In diseases with *airway obstruction*, it is usually much more difficult to expire than to inspire because the closing tendency of the airways is greatly increased by the extra

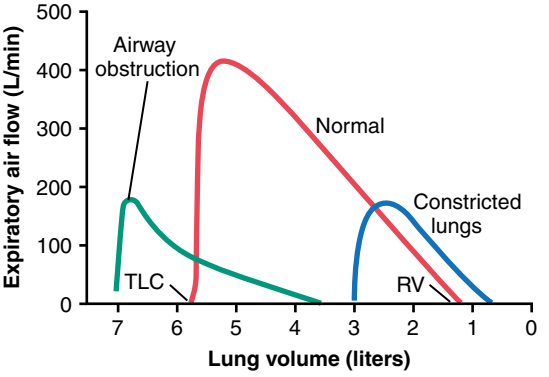


Figure 42-2 Effect of two respiratory abnormalities—constricted lungs and airway obstruction—on the maximum expiratory flow-volume curve. TLC, total lung capacity; RV, residual volume.

positive pressure required in the chest to cause expiration. By contrast, the extra negative pleural pressure that occurs during inspiration actually "pulls" the airways open at the same time that it expands the alveoli. Therefore, air tends to enter the lung easily but then becomes trapped in the lungs. Over a period of months or years, this effect increases both the TLC and the RV, as shown by the green curve in Figure 42-2. Also, because of the obstruction of the airways and because they collapse more easily than normal airways, the maximum expiratory flow rate is greatly reduced.

The classic disease that causes severe airway obstruction is *asthma*. Serious airway obstruction also occurs in some stages of *emphysema*.

Forced Expiratory Vital Capacity and Forced Expiratory Volume

Another exceedingly useful clinical pulmonary test, and one that is also simple, is to record on a spirometer the *forced expiratory vital capacity* (FVC). Such a recording is shown in Figure 42-3*A* for a person with normal lungs and in Figure 42-3*B* for a person with partial airway obstruction. In performing the FVC maneuver, the person first inspires maximally to the total lung capacity and then exhales into the spirometer with maximum expiratory effort as rapidly and as completely as possible. The total distance of the downslope of the lung volume record represents the FVC, as shown in the figure.

Now, study the difference between the two records (1) for normal lungs and (2) for *partial* airway obstruction. The total volume changes of the FVCs are not greatly different, indicating only a moderate difference in basic lung volumes in the two persons. There is, however, a *major difference in the amounts of air that these persons can expire each second*, especially during the first second. Therefore, it is customary to compare the recorded forced expiratory volume during the first second (FEV_1) with the normal. In the normal person (see Figure 42-3*A*), the percentage of the FVC that is expired in the first second divided by the total FVC (FEV_1/FVC%) is 80 percent. However, note in Figure 42-3*B* that, with airway obstruction, this value decreased to only 47 percent. In serious airway obstruction, as often occurs in acute asthma, this can decrease to less than 20 percent.

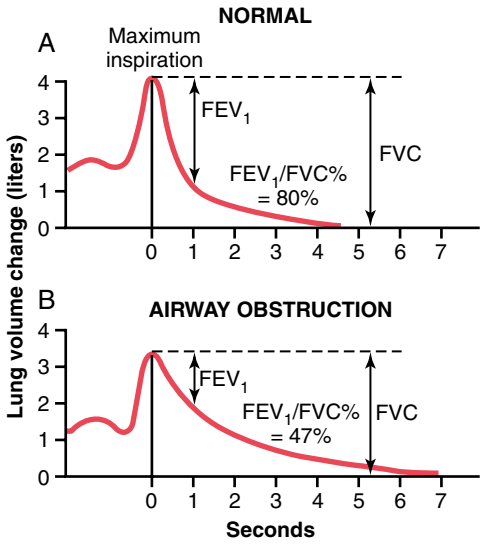


Figure 42-3 Recordings during the forced vital capacity maneuver: *A*, in a healthy person and *B*, in a person with partial airway obstruction. (The "zero" on the volume scale is residual volume.)

Pathophysiology of Specific Pulmonary Abnormalities

Chronic Pulmonary Emphysema

The term *pulmonary emphysema* literally means excess air in the lungs. However, this term is usually used to describe complex obstructive and destructive process of the lungs caused by many years of smoking. It results from the following major pathophysiologic changes in the lungs:

1. *Chronic infection*, caused by inhaling smoke or other substances that irritate the bronchi and bronchioles. The chronic infection seriously deranges the normal protective mechanisms of the airways, including partial paralysis of the cilia of the respiratory epithelium, an effect caused by nicotine. As a result, mucus cannot be moved easily out of the passageways. Also, stimulation of excess mucus secretion occurs, which further exacerbates the condition. Inhibition of the alveolar macrophages also occurs, so they become less effective in combating infection.
2. The infection, excess mucus, and inflammatory edema of the bronchiolar epithelium together cause *chronic obstruction* of many of the smaller airways.
3. The obstruction of the airways makes it especially difficult to expire, thus causing *entrapment of air in the alveoli* and overstretching them. This, combined with the lung infection, causes *marked destruction of as much as 50 to 80 percent of the alveolar walls*. Therefore, the final picture of the emphysematous lung is that shown in Figures 42-4 *(top)* and 42-5.

The physiologic effects of chronic emphysema are variable, depending on the severity of the disease and the relative degrees of bronchiolar obstruction versus lung parenchymal destruction. Among the different abnormalities are the following:

1. The bronchiolar obstruction *increases airway resistance* and results in greatly increased work of breathing. It is especially difficult for the person to move air through the bronchioles during expiration because the compressive force on the outside of the lung not only compresses the alveoli but also compresses the bronchioles, which further increases their resistance during expiration.

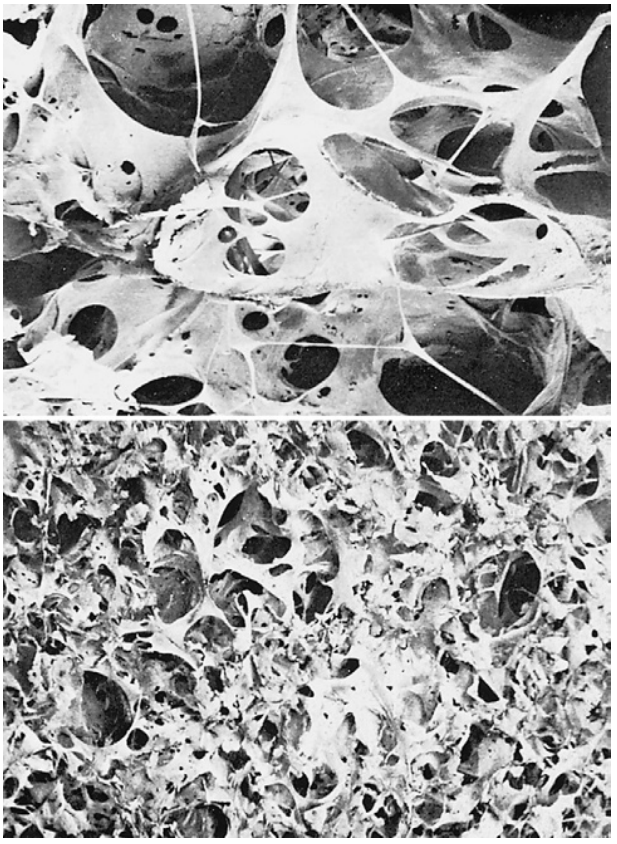


Figure 42-4 Contrast of the emphysematous lung (***top figure***) with the normal lung (***bottom figure***), showing extensive alveolar destruction in emphysema. (Reproduced with permission of Patricia Delaney and the Department of Anatomy, The Medical College of Wisconsin.)

2. The marked loss of alveolar walls greatly *decreases the diffusing capacity* of the lung, which reduces the ability of the lungs to oxygenate the blood and remove carbon dioxide from the blood.
3. The obstructive process is frequently much worse in some parts of the lungs than in other parts, so some portions of the lungs are well ventilated, whereas other portions are poorly ventilated. This often causes *extremely abnormal ventilation-perfusion ratios*, with a very low $\dot{V}a/\dot{Q}$ in some parts *(physiologic shunt)*, resulting in poor aeration of the blood, and very high $\dot{V}a/\dot{Q}$ in other parts *(physiologic dead space)*, resulting in wasted ventilation, both effects occurring in the same lungs.
4. Loss of large portions of the alveolar walls also decreases the number of pulmonary capillaries through which blood can pass. As a result, the pulmonary vascular resistance often increases markedly, causing *pulmonary hypertension*. This in turn overloads the right side of the heart and frequently causes right-sided heart failure.

Chronic emphysema usually progresses slowly over many years. The person develops both hypoxia and hypercapnia because of hypoventilation of many alveoli plus loss of alveolar walls. The net result of all these effects is severe, prolonged, devastating *air hunger* that can last for years until the hypoxia and hypercapnia cause death—a high penalty to pay for smoking.

Pneumonia

The term *pneumonia* includes any inflammatory condition of the lung in which some or all of the alveoli are filled with fluid and blood cells, as shown in Figure 42-5. A common type of pneumonia is *bacterial pneumonia*, caused most frequently by *pneumococci*. This disease begins with infection in the alveoli; the pulmonary membrane becomes inflamed and highly porous so that fluid and even red and white blood cells leak out of the blood into the alveoli. Thus, the infected alveoli become progressively filled with fluid and cells, and the infection spreads by extension of bacteria or virus from alveolus to alveolus. Eventually, large areas of the lungs, sometimes whole lobes or even a whole lung, become "consolidated," which means that they are filled with fluid and cellular debris.

In pneumonia, the gas exchange functions of the lungs decline in different stages of the disease. In early stages, the pneumonia process might well be localized to only one lung, with alveolar ventilation reduced while blood flow through the lung continues normally. This causes two major pulmonary abnormalities: (1) reduction in the total available surface area of the respiratory membrane

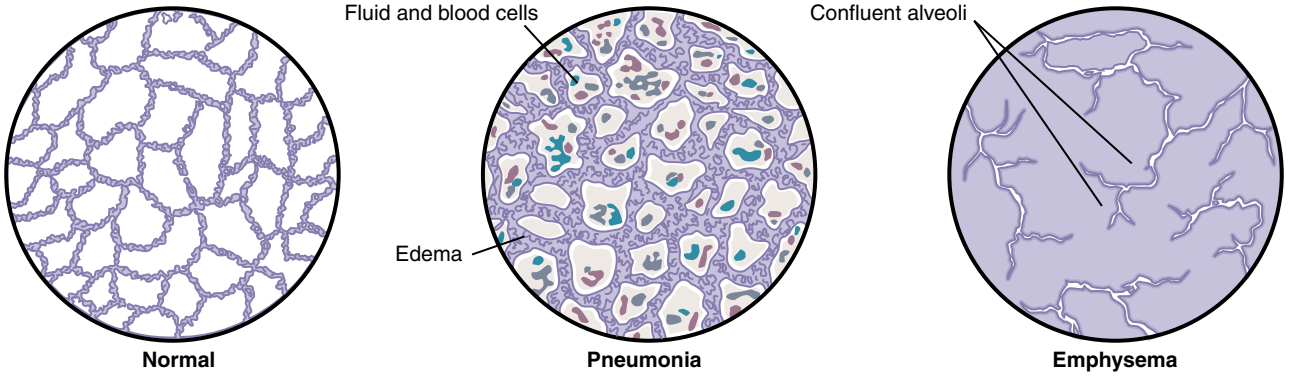


Figure 42-5 Lung alveolar changes in pneumonia and emphysema.

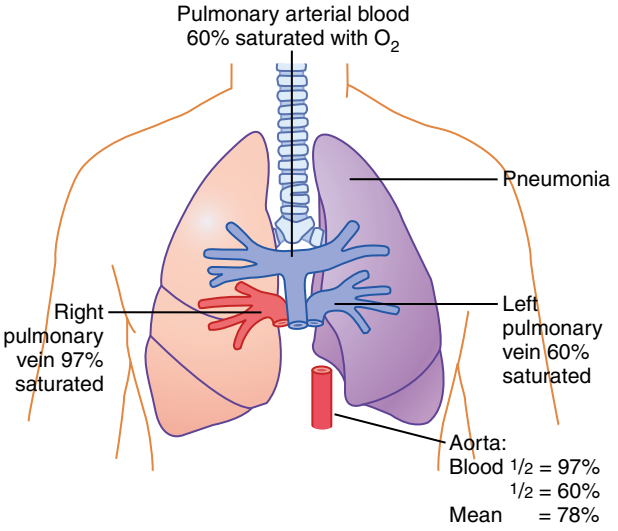


Figure 42-6 Effect of pneumonia on percentage saturation of oxygen in the pulmonary artery, the right and left pulmonary veins, and the aorta.

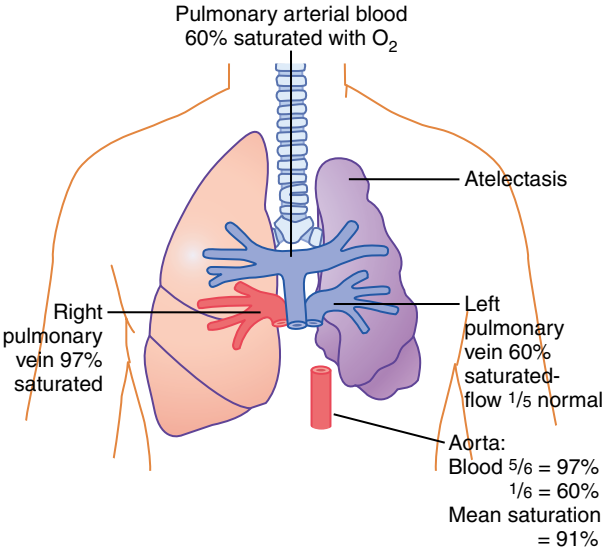


Figure 42-7 Effect of atelectasis on aortic blood oxygen saturation.

and (2) decreased ventilation-perfusion ratio. Both these effects cause *hypoxemia* (low blood oxygen) and *hypercapnia* (high blood carbon dioxide).

Figure 42-6 shows the effect of the decreased ventilation-perfusion ratio in pneumonia, showing that the blood passing through the aerated lung becomes 97 percent saturated with oxygen, whereas that passing through the unaerated lung is about 60 percent saturated. Therefore, the average saturation of the blood pumped by the left heart into the aorta is only about 78 percent, which is far below normal.

Atelectasis

Atelectasis means collapse of the alveoli. It can occur in localized areas of a lung or in an entire lung. Common causes of atelectasis are (1) total obstruction of the airway or (2) lack of surfactant in the fluids lining the alveoli.

Airway Obstruction Causes Lung Collapse. The airway obstruction type of atelectasis usually results from (1) blockage of many small bronchi with mucus or (2) obstruction of a major bronchus by either a large mucus plug or some solid object such as a tumor. The air entrapped beyond the block is absorbed within minutes to hours by the blood flowing in the pulmonary capillaries. If the lung tissue is pliable enough, this will lead simply to collapse of the alveoli. However, if the lung is rigid because of fibrotic tissue and cannot collapse, absorption of air from the alveoli creates very negative pressures within the alveoli, which pull fluid out of the pulmonary capillaries into the alveoli, thus causing the alveoli to fill completely with edema fluid. This almost always is the effect that occurs when an entire lung becomes atelectatic, a condition called *massive collapse* of the lung.

The effects on overall pulmonary function caused by *massive collapse* (atelectasis) of an entire lung are shown in Figure 42-7. Collapse of the lung tissue not only occludes the alveoli but also almost always increases the *resistance to blood flow* through the pulmonary vessels of the collapsed lung. This resistance increase occurs partially because of the lung collapse itself, which compresses and folds the vessels as the volume of the lung decreases. In addition, hypoxia in the collapsed alveoli causes additional vasoconstriction, as explained in Chapter 38.

Because of the vascular constriction, blood flow through the atelectatic lung is greatly reduced. Fortunately, most of the blood is routed through the ventilated lung and therefore becomes well aerated. In the situation shown in Figure 42-7, five sixths of the blood passes through the aerated lung and only one sixth through the unaerated lung. As a result, the overall ventilation-perfusion ratio is only moderately compromised, so the aortic blood has only mild oxygen desaturation despite total loss of ventilation in an entire lung.

Lack of "Surfactant" as a Cause of Lung Collapse. The secretion and function of *surfactant* in the alveoli were discussed in Chapter 37. It was pointed out that the surfactant is secreted by special alveolar epithelial cells into the fluids that coat the inside surface of the alveoli. The surfactant in turn decreases the surface tension in the alveoli 2- to 10-fold, which normally plays a major role in preventing alveolar collapse. However, in a number of conditions, such as in *hyaline membrane disease* (also called *respiratory distress syndrome*), which often occurs in newborn premature babies, the quantity of surfactant secreted by the alveoli is so greatly depressed that the surface tension of the alveolar fluid becomes several times normal. This causes a serious tendency for the lungs of these babies to collapse or to become filled with fluid. As explained in Chapter 37, many of these infants die of suffocation when large portions of the lungs become atelectatic.

Asthma—Spasmodic Contraction of Smooth Muscles in Bronchioles

Asthma is characterized by spastic contraction of the smooth muscle in the bronchioles, which partially obstructs the bronchioles and causes extremely difficult breathing. It occurs in 3 to 5 percent of all people at some time in life.

The usual cause of asthma is contractile hypersensitivity of the bronchioles in response to foreign substances in the air. In about 70 percent of patients younger than age 30 years, the asthma is caused by allergic hypersensitivity, especially sensitivity to plant pollens. In older people, the cause is almost always hypersensitivity to nonallergenic types of irritants in the air, such as irritants in smog.

The allergic reaction that occurs in the allergic type of asthma is believed to occur in the following way: The typical allergic person tends to form abnormally large amounts of IgE antibodies, and these antibodies cause allergic reactions when they react with the specific antigens that have caused them to develop in the first place, as explained in Chapter 34. In asthma, these *antibodies are mainly attached to mast cells* that are present in the lung interstitium in close association with the bronchioles and small bronchi. When the asthmatic person breathes in pollen to which he or she is sensitive (i.e., to which the person has developed IgE antibodies), the pollen reacts with the mast cell–attached antibodies and causes the mast cells to release several different substances. Among them are (a) *histamine*, (b) *slow-reacting substance of anaphylaxis* (which is a mixture of leukotrienes), (c) *eosinophilic chemotactic factor*, and (d) *bradykinin*. The combined effects of all these factors, especially the slow-reacting substance of anaphylaxis, are to produce (1) localized edema in the walls of the small bronchioles, as well as secretion of thick mucus into the bronchiolar lumens, and (2) spasm of the bronchiolar smooth muscle. Therefore, the airway resistance increases greatly.

As discussed earlier in this chapter, the bronchiolar diameter becomes more reduced during expiration than during inspiration in asthma, caused by bronchiolar collapse during expiratory effort that compresses the outsides of the bronchioles. Because the bronchioles of the asthmatic lungs are already partially occluded, further occlusion resulting from the external pressure creates especially severe obstruction during expiration. That is, the asthmatic person often can inspire quite adequately but has great difficulty expiring. Clinical measurements show (1) greatly reduced maximum expiratory rate and (2) reduced timed expiratory volume. Also, all of this together results in dyspnea, or "air hunger," which is discussed later in this chapter.

The *functional residual capacity* and *residual volume* of the lung become especially increased during the acute asthmatic attack because of the difficulty in expiring air from the lungs. Also, over a period of years, the chest cage becomes permanently enlarged, causing a "barrel chest," and both the functional residual capacity and lung residual volume become permanently increased.

Tuberculosis

In tuberculosis, the tubercle bacilli cause a peculiar tissue reaction in the lungs, including (1) invasion of the infected tissue by macrophages and (2) "walling off" of the lesion by fibrous tissue to form the so-called *tubercle*. This walling-off process helps to limit further transmission of the tubercle bacilli in the lungs and therefore is part of the protective process against extension of the infection. However, in about 3 percent of all people who develop tuberculosis, if untreated, the walling-off process fails and tubercle bacilli spread throughout the lungs, often causing extreme destruction of lung tissue with formation of large abscess cavities.

Thus, tuberculosis in its late stages is characterized by many areas of fibrosis throughout the lungs, as well as reduced total amount of functional lung tissue. These effects cause (1) *increased "work"* on the part of the respiratory muscles to cause pulmonary ventilation and *reduced vital capacity and breathing capacity*; (2) *reduced total respiratory membrane surface area* and *increased thickness of the respiratory membrane*, causing progressively *diminished pulmonary diffusing capacity*; and (3) *abnormal ventilation-perfusion ratio* in the lungs, further reducing overall pulmonary diffusion of oxygen and carbon dioxide.

Hypoxia and Oxygen Therapy

Almost any of the conditions discussed in the past few sections of this chapter can cause serious degrees of cellular hypoxia throughout the body. Sometimes, oxygen therapy is of great value; other times, it is of moderate value; and, at still other times, it is of almost no value. Therefore, it is important to understand the different types of hypoxia; then we can discuss the physiologic principles of oxygen therapy. The following is a descriptive classification of the causes of hypoxia:

1. Inadequate oxygenation of the blood in the lungs because of extrinsic reasons
   - **a.** Deficiency of oxygen in the atmosphere
   - **b.** Hypoventilation (neuromuscular disorders)
2. Pulmonary disease
   - **a.** Hypoventilation caused by increased airway resistance or decreased pulmonary compliance
   - **b.** Abnormal alveolar ventilation-perfusion ratio (including either increased physiologic dead space or increased physiologic shunt)
   - **c.** Diminished respiratory membrane diffusion
3. Venous-to-arterial shunts ("right-to-left" cardiac shunts)
4. Inadequate oxygen transport to the tissues by the blood
   - **a.** Anemia or abnormal hemoglobin
   - **b.** General circulatory deficiency

c. Localized circulatory deficiency (peripheral, cerebral, coronary vessels)

d. Tissue edema

5. Inadequate tissue capability of using oxygen

a. Poisoning of cellular oxidation enzymes

b. Diminished cellular metabolic capacity for using oxygen, because of toxicity, vitamin deficiency, or other factors

This classification of the types of hypoxia is mainly self-evident from the discussions earlier in the chapter. Only one type of hypoxia in the classification needs further elaboration: the hypoxia caused by inadequate capability of the body's tissue cells to use oxygen.

Inadequate Tissue Capability to Use Oxygen. The classic cause of inability of the tissues to use oxygen is *cyanide poisoning*, in which the action of the enzyme *cytochrome oxidase* is completely blocked by the cyanide—to such an extent that the tissues simply cannot use oxygen even when plenty is available. Also, deficiencies of some of the *tissue cellular oxidative enzymes* or of other elements in the tissue oxidative system can lead to this type of hypoxia. A special example occurs in the disease *beriberi*, in which several important steps in tissue utilization of oxygen and formation of carbon dioxide are compromised because of *vitamin B deficiency*.

Effects of Hypoxia on the Body. Hypoxia, if severe enough, can cause death of cells throughout the body, but in less severe degrees it causes principally (1) depressed mental activity, sometimes culminating in coma, and (2) reduced work capacity of the muscles. These effects are specifically discussed in Chapter 43 in relation to high-altitude physiology.

Oxygen Therapy in Different Types of Hypoxia

Oxygen can be administered by (1) placing the patient's head in a "tent" that contains air fortified with oxygen, (2) allowing the patient to breathe either pure oxygen or high concentrations of oxygen from a mask, or (3) administering oxygen through an intranasal tube.

Recalling the basic physiologic principles of the different types of hypoxia, one can readily decide when oxygen therapy will be of value and, if so, how valuable.

In *atmospheric hypoxia*, oxygen therapy can completely correct the depressed oxygen level in the inspired gases and, therefore, provide 100 percent effective therapy.

In *hypoventilation hypoxia*, a person breathing 100 percent oxygen can move five times as much oxygen into the alveoli with each breath as when breathing normal air. Therefore, here again oxygen therapy can be extremely beneficial. (However, this provides no benefit for the excess blood carbon dioxide also caused by the hypoventilation.)

In *hypoxia caused by impaired alveolar membrane diffusion*, essentially the same result occurs as in hypoventilation hypoxia because oxygen therapy can increase the

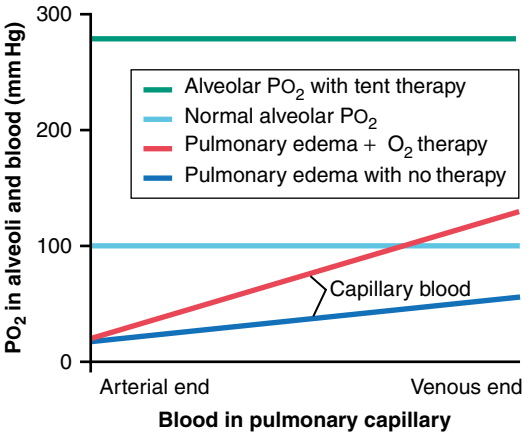


Figure 42-8 Absorption of oxygen into the pulmonary capillary blood in pulmonary edema with and without oxygen tent therapy.

P_{O_2} in the lung alveoli from the normal value of about 100 mm Hg to as high as 600 mm Hg. This raises the oxygen pressure gradient for diffusion of oxygen from the alveoli to the blood from the normal value of 60 mm Hg to as high as 560 mm Hg, an increase of more than 800 percent. This highly beneficial effect of oxygen therapy in diffusion hypoxia is demonstrated in Figure 42-8, which shows that the pulmonary blood in this patient with pulmonary edema picks up oxygen three to four times as rapidly as would occur with no therapy.

In *hypoxia caused by anemia, abnormal hemoglobin transport of oxygen, circulatory deficiency, or physiologic shunt*, oxygen therapy is of much less value because normal oxygen is already available in the alveoli. The problem instead is that one or more of the mechanisms for transporting oxygen from the lungs to the tissues are deficient. Even so, a small amount of extra oxygen, between 7 and 30 percent, can be *transported in the dissolved state* in the blood when alveolar oxygen is increased to maximum even though the amount transported by the hemoglobin is hardly altered. This small amount of extra oxygen may be the difference between life and death.

In the different types of *hypoxia caused by inadequate tissue use of oxygen*, there is abnormality neither of oxygen pickup by the lungs nor of transport to the tissues. Instead, the tissue metabolic enzyme system is simply incapable of using the oxygen that is delivered. Therefore, oxygen therapy provides no measurable benefit.

Cyanosis

The term *cyanosis* means blueness of the skin, and its cause is excessive amounts of deoxygenated hemoglobin in the skin blood vessels, especially in the capillaries. This deoxygenated hemoglobin has an intense dark blue–purple color that is transmitted through the skin.

In general, definite cyanosis appears whenever the *arterial blood* contains more than 5 grams of deoxygenated hemoglobin in each 100 milliliters of blood. A person with *anemia* almost never becomes cyanotic because there is not enough hemoglobin for 5 grams to be deoxygenated

in 100 milliliters of arterial blood. Conversely, in a person with excess red blood cells, as occurs in *polycythemia vera*, the great excess of available hemoglobin that can become deoxygenated leads frequently to cyanosis, even under otherwise normal conditions.

Hypercapnia—Excess Carbon Dioxide in the Body Fluids

One might suspect, on first thought, that any respiratory condition that causes hypoxia would also cause hypercapnia. However, hypercapnia usually occurs in association with hypoxia only when the hypoxia is caused by *hypoventilation* or *circulatory deficiency*. The reasons for this are the following.

Hypoxia caused by *too little oxygen in the air, too little hemoglobin*, or *poisoning of the oxidative enzymes* has to do only with the availability of oxygen or use of oxygen by the tissues. Therefore, it is readily understandable that hypercapnia is *not* a concomitant of these types of hypoxia.

In hypoxia resulting from poor diffusion through the pulmonary membrane or through the tissues, serious hypercapnia usually does not occur at the same time because carbon dioxide diffuses 20 times as rapidly as oxygen. If hypercapnia does begin to occur, this immediately stimulates pulmonary ventilation, which corrects the hypercapnia but not necessarily the hypoxia.

Conversely, in hypoxia caused by hypoventilation, carbon dioxide transfer between the alveoli and the atmosphere is affected as much as is oxygen transfer. Hypercapnia then occurs along with the hypoxia. And in circulatory deficiency, diminished flow of blood decreases carbon dioxide removal from the tissues, resulting in tissue hypercapnia in addition to tissue hypoxia. However, the transport capacity of the blood for carbon dioxide is more than three times that for oxygen, so that the resulting tissue hypercapnia is much less than the tissue hypoxia.

When the alveolar P_{CO_2} rises above about 60 to 75 mm Hg, an otherwise normal person by then is breathing about as rapidly and deeply as he or she can, and "air hunger," also called *dyspnea*, becomes severe.

If the P_{CO_2} rises to 80 to 100 mm Hg, the person becomes lethargic and sometimes even semicomatose. Anesthesia and death can result when the P_{CO_2} rises to 120 to 150 mm Hg. At these higher levels of P_{CO_2}, the excess carbon dioxide now begins to depress respiration rather than stimulate it, thus causing a vicious circle: (1) more carbon dioxide, (2) further decrease in respiration, (3) then more carbon dioxide, and so forth—culminating rapidly in a respiratory death.

Dyspnea

Dyspnea means mental anguish associated with inability to ventilate enough to satisfy the demand for air. A common synonym is *air hunger*.

At least three factors often enter into the development of the sensation of dyspnea. They are (1) abnormality of respiratory gases in the body fluids, especially hypercapnia and, to a much less extent, hypoxia; (2) the amount of work that must be performed by the respiratory muscles to provide adequate ventilation; and (3) state of mind.

A person becomes very dyspneic, especially from excess buildup of carbon dioxide in the body fluids. At times, however, the levels of both carbon dioxide and oxygen in the body fluids are normal, but to attain this normality of the respiratory gases, the person has to breathe forcefully. In these instances, the forceful activity of the respiratory muscles frequently gives the person a sensation of dyspnea.

Finally, the person's respiratory functions may be normal and still dyspnea may be experienced because of an abnormal state of mind. This is called *neurogenic dyspnea* or *emotional dyspnea*. For instance, almost anyone momentarily thinking about the act of breathing may suddenly start taking breaths a little more deeply than ordinarily because of a feeling of mild dyspnea. This feeling is greatly enhanced in people who have a psychological fear of not being able to receive a sufficient quantity of air, such as on entering small or crowded rooms.

Artificial Respiration

Resuscitator. Many types of respiratory resuscitators are available, and each has its own characteristic principles of operation. The resuscitator shown in Figure 42-9*A* consists of a tank supply of oxygen or air; a mechanism for applying intermittent positive pressure and, with some

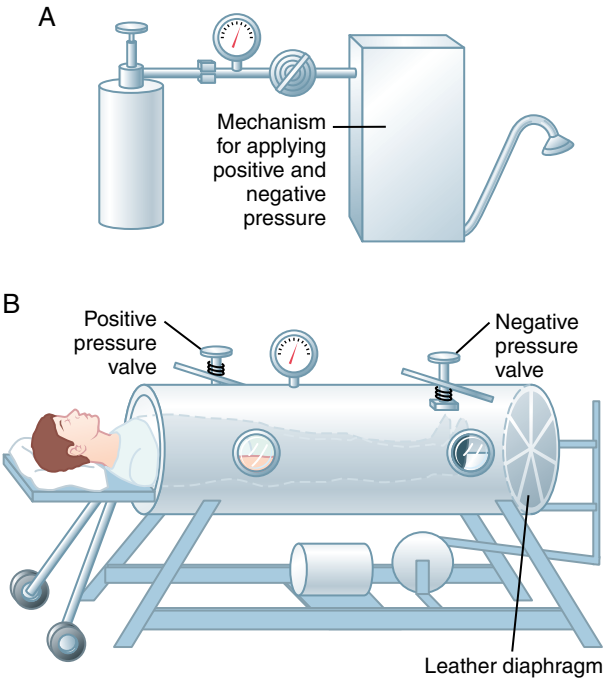


Figure 42-9 *A*, Resuscitator. *B*, Tank respirator.

machines, negative pressure as well; and a mask that fits over the face of the patient or a connector for joining the equipment to an endotracheal tube. This apparatus forces air through the mask or endotracheal tube into the lungs of the patient during the positive-pressure cycle of the resuscitator and then usually allows the air to flow passively out of the lungs during the remainder of the cycle.

Earlier resuscitators often caused damage to the lungs because of excessive positive pressure. Their usage was at one time greatly decried. However, resuscitators now have adjustable positive-pressure limits that are commonly set at 12 to 15 cm H_2O pressure for normal lungs (but sometimes much higher for noncompliant lungs).

Tank Respirator (the "Iron-Lung"). Figure 42-9*B* shows the tank respirator with a patient's body inside the tank and the head protruding through a flexible but airtight collar. At the end of the tank opposite the patient's head, a motor-driven leather diaphragm moves back and forth with sufficient excursion to raise and lower the pressure inside the tank. As the leather diaphragm moves inward, positive pressure develops around the body and causes expiration; as the diaphragm moves outward, negative pressure causes inspiration. Check valves on the respirator control the positive and negative pressures. Ordinarily these pressures are adjusted so that the negative pressure that causes inspiration falls to −10 to −20 cm H_2O and the positive pressure rises to 0 to +5 cm H_2O.

Effect of the Resuscitator and the Tank Respirator on Venous Return. When air is forced into the lungs under positive pressure by a resuscitator, or when the pressure around the patient's body is *reduced* by the tank respirator, the pressure inside the lungs becomes greater than pressure everywhere else in the body. Flow of blood into the chest and heart from the peripheral veins becomes impeded. As a result, use of excessive pressures with either the resuscitator or the tank respirator can reduce the cardiac output—sometimes to lethal levels. For instance, continuous exposure for more than a few minutes to greater than 30 mm Hg positive pressure in the lungs can cause death because of inadequate venous return to the heart.

Bibliography

Albert R, Spiro S, Jett J: *Comprehensive Respiratory Medicine*, Philadelphia, 2002, Mosby.

Barnes PJ: The cytokine network in asthma and chronic obstructive pulmonary disease, *J Clin Invest* 118:3546, 2008.

Cardoso WV: Molecular regulation of lung development, *Annu Rev Physiol* 63:471, 2001.

Casey KR, Cantillo KO, Brown LK: Sleep-related hypoventilation/hypoxemic syndromes, *Chest* 131:1936, 2007.

Eder W, Ege MJ, von Mutius E: The asthma epidemic, *N Engl J Med* 355:2226, 2006.

Herzog EL, Brody AR, Colby TV, et al: Knowns and unknowns of the alveolus, *Proc Am Thorac Soc* 5:778, 2008.

Knight DA, Holgate ST: The airway epithelium: structural and functional properties in health and disease, *Respirology* 8:432, 2003.

McConnell AK, Romer LM: Dyspnoea in health and obstructive pulmonary disease: the role of respiratory muscle function and training, *Sports Med* 34:117, 2004.

Mühlfeld C, Rothen-Rutishauser B, Blank F, et al: Interactions of nanoparticles with pulmonary structures and cellular responses, *Am J Physiol Lung Cell Mol Physiol* 294:L817, 2008.

Naureckas ET, Solway J: Clinical practice. Mild asthma, *N Engl J Med* 345:1257, 2001.

Ramanathan R: Optimal ventilatory strategies and surfactant to protect the preterm lungs, *Neonatology* 93:302, 2008.

Sharafkhaneh A, Hanania NA, Kim V: Pathogenesis of emphysema: from the bench to the bedside, *Proc Am Thorac Soc* 5:475, 2008.

Sin DD, McAlister FA, Man SF, et al: Contemporary management of chronic obstructive pulmonary disease: scientific review, *JAMA* 290:2301, 2003.

Soni N, Williams P: Positive pressure ventilation: what is the real cost? *Br J Anaesth* 101:446, 2008.

Taraseviciene-Stewart L, Voelkel NF: Molecular pathogenesis of emphysema, *J Clin Invest* 118:394, 2008.

Whitsett JA, Weaver TE: Hydrophobic surfactant proteins in lung function and disease, *N Engl J Med* 347:2141, 2002.

Wills-Karp M, Ewart SL: Time to draw breath: asthma-susceptibility genes are identified, *Nat Rev Genet* 5:376, 2004.

Wright JL, Cosio M, Churg A: Animal models of chronic obstructive pulmonary disease, *Am J Physiol Lung Cell Mol Physiol* 295:L1, 2008.

CHAPTER 43

Aviation, High Altitude, and Space Physiology

As humans have ascended to higher and higher altitudes in aviation, mountain climbing, and space vehicles, it has become progressively more important to understand the effects of altitude and low gas pressures on the human body. This chapter deals with these problems, as well as acceleratory forces, weightlessness, and other challenges to body homeostasis that occur at high altitude and in space flight.

Effects of Low Oxygen Pressure on the Body

Barometric Pressures at Different Altitudes. Table 43-1 gives the approximate *barometric* and *oxygen pressures* at different altitudes, showing that at sea level, the barometric pressure is 760 mm Hg; at 10,000 feet, only 523 mm Hg; and at 50,000 feet, 87 mm Hg. This decrease in barometric pressure is the basic cause of all the hypoxia problems in high-altitude physiology because, as the barometric pressure decreases, the atmospheric oxygen partial pressure (P_{O_2}) decreases proportionately, remaining at all times slightly less than 21 percent of the total barometric pressure; at sea level P_{O_2} is about 159 mm Hg, but at 50,000 feet P_{O_2} is only 18 mm Hg.

Alveolar P_{O_2} at Different Elevations

Carbon Dioxide and Water Vapor Decrease the Alveolar Oxygen. Even at high altitudes, carbon dioxide is continually excreted from the pulmonary blood into the alveoli. Also, water vaporizes into the inspired air from the respiratory surfaces. These two gases dilute the oxygen in the alveoli, thus reducing the oxygen concentration. Water vapor pressure in the alveoli remains at 47 mm Hg as long as the body temperature is normal, regardless of altitude.

In the case of carbon dioxide, during exposure to very high altitudes, the alveolar P_{CO_2} falls from the sea-level value of 40 mm Hg to lower values. In the *acclimatized* person, who increases his or her ventilation about fivefold, the P_{CO_2} falls to about 7 mm Hg because of increased respiration.

Now let us see how the pressures of these two gases affect the alveolar oxygen. For instance, assume that the barometric pressure falls from the normal sea-level value of 760 mm Hg to 253 mm Hg, which is the usual measured value at the top of 29,028-foot Mount Everest. Forty-seven mm Hg of this must be water vapor, leaving only 206 mm Hg for all the other gases. In the *acclimatized* person, 7 mm of the 206 mm Hg must be carbon dioxide, leaving only 199 mm Hg. If there were no use of oxygen by the body, one fifth of this 199 mm Hg would be oxygen and four fifths would be nitrogen; that is, the P_{O_2} in the alveoli would be 40 mm Hg. However, some of this remaining alveolar oxygen is continually being absorbed into the blood, leaving about 35 mm Hg oxygen pressure in the alveoli. At the summit of Mount Everest, only the best of acclimatized people can barely survive when breathing air. But the effect is very different when the person is breathing pure oxygen, as we see in the following discussions.

Alveolar P_{O_2} at Different Altitudes. The fifth column of Table 43-1 shows the approximate P_{O_2}s in the alveoli at different altitudes when one is breathing air for both the *unacclimatized* and the *acclimatized* person. At sea level, the alveolar P_{O_2} is 104 mm Hg; at 20,000 feet altitude, it falls to about 40 mm Hg in the unacclimatized person but only to 53 mm Hg in the acclimatized person. The difference between these two is that alveolar ventilation increases much more in the acclimatized person than in the unacclimatized person, as we discuss later.

Saturation of Hemoglobin with Oxygen at Different Altitudes. Figure 43-1 shows arterial blood oxygen saturation at different altitudes while a person is breathing air and while breathing oxygen. Up to an altitude of about 10,000 feet, even when air is breathed, the arterial oxygen saturation remains at least as high as 90 percent. Above 10,000 feet, the arterial oxygen saturation falls rapidly, as shown by the blue curve of the figure, until it is slightly less than 70 percent at 20,000 feet and much less at still higher altitudes.

Table 43-1 Effects of Acute Exposure to Low Atmospheric Pressures on Alveolar Gas Concentrations and Arterial Oxygen Saturation*

Altitude (ft/meters)	Barometric Pressure (mm Hg)	P_{O_2} in Air (mm Hg)	Breathing Air			Breathing Pure Oxygen		
			P_{CO_2} in Alveoli (mm Hg)	*P_{O_2} in Alveoli (mm Hg)*	*Arterial Oxygen Saturation (%)*	*P_{CO_2} in Alveoli (mm Hg)*	*P_{O_2} in Alveoli (mm Hg)*	*Arterial Oxygen Saturation (%)*
0	760	159	40 (40)	104 (104)	97 (97)	40	673	100
10,000/3048	523	110	36 (23)	67 (77)	90 (92)	40	436	100
20,000/6096	349	73	24 (10)	40 (53)	73 (85)	40	262	100
30,000/9144	226	47	24 (7)	18 (30)	24 (38)	40	139	99
40,000/12,192	141	29				36	58	84
50,000/15,240	87	18				24	16	15

*Numbers in parentheses are acclimatized values.

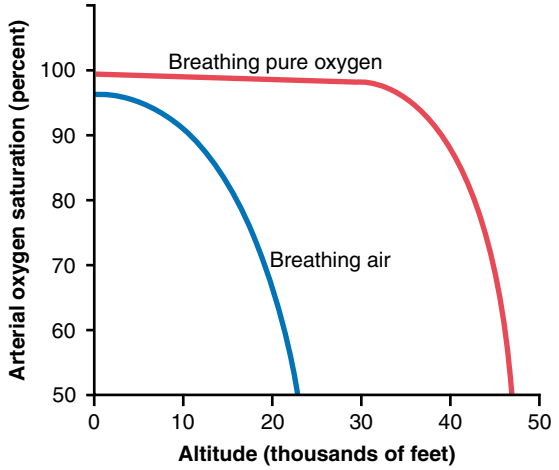


Figure 43-1 Effect of high altitude on arterial oxygen saturation when breathing air and when breathing pure oxygen.

Effect of Breathing Pure Oxygen on Alveolar P_{O_2} at Different Altitudes

When a person breathes pure oxygen instead of air, most of the space in the alveoli formerly occupied by nitrogen becomes occupied by oxygen. At 30,000 feet, an aviator could have an alveolar P_{O_2} as high as 139 mm Hg instead of the 18 mm Hg when breathing air (see Table 43-1).

The red curve of Figure 43-1 shows arterial blood hemoglobin oxygen saturation at different altitudes when one is breathing pure oxygen. Note that the saturation remains above 90 percent until the aviator ascends to about 39,000 feet; then it falls rapidly to about 50 percent at about 47,000 feet.

The "Ceiling" When Breathing Air and When Breathing Oxygen in an Unpressurized Airplane

Comparing the two arterial blood oxygen saturation curves in Figure 43-1, one notes that an aviator breathing pure oxygen in an unpressurized airplane can ascend to far higher altitudes than one breathing air. For instance, the arterial saturation at 47,000 feet when one is breathing oxygen is about 50 percent and is equivalent to the arterial oxygen saturation at 23,000 feet when one is breathing air. In addition, because an unacclimatized person usually can remain conscious until the arterial oxygen saturation falls to 50 percent, for short exposure times the ceiling for an aviator in an unpressurized airplane when breathing air is about 23,000 feet and when breathing pure oxygen is about 47,000 feet, provided the oxygen-supplying equipment operates perfectly.

Acute Effects of Hypoxia

Some of the important acute effects of hypoxia in the unacclimatized person breathing air, beginning at an altitude of about 12,000 feet, are drowsiness, lassitude, mental and muscle fatigue, sometimes headache, occasionally nausea, and sometimes euphoria. These effects progress to a stage of twitchings or seizures above 18,000 feet and end, above 23,000 feet in the unacclimatized person, in coma, followed shortly thereafter by death.

One of the most important effects of hypoxia is decreased mental proficiency, which decreases judgment, memory, and performance of discrete motor movements. For instance, if an unacclimatized aviator stays at 15,000 feet for 1 hour, mental proficiency ordinarily falls to about 50 percent of normal, and after 18 hours at this level it falls to about 20 percent of normal.

Acclimatization to Low P_{O_2}

A person remaining at high altitudes for days, weeks, or years becomes more and more *acclimatized* to the low P_{O_2}, so it causes fewer deleterious effects on the body. And it becomes possible for the person to work harder without hypoxic effects or to ascend to still higher altitudes.

The principal means by which acclimatization comes about are (1) a great increase in pulmonary ventilation, (2) increased numbers of red blood cells, (3) increased diffusing capacity of the lungs, (4) increased vascularity of the

peripheral tissues, and (5) increased ability of the tissue cells to use oxygen despite low P_{O_2}.

Increased Pulmonary Ventilation—Role of Arterial Chemoreceptors. Immediate exposure to low P_{O_2} stimulates the arterial chemoreceptors, and this increases alveolar ventilation to a maximum of about 1.65 times normal. Therefore, compensation occurs within seconds for the high altitude, and it alone allows the person to rise several thousand feet higher than would be possible without the increased ventilation. Then, if the person remains at very high altitude for several days, the chemoreceptors increase ventilation still more, up to about five times normal.

The immediate increase in pulmonary ventilation on rising to a high altitude blows off large quantities of carbon dioxide, reducing the P_{CO_2} and increasing the pH of the body fluids. These changes *inhibit* the brain stem respiratory center and thereby *oppose the effect of low* P_{O_2} *to stimulate respiration by way of the peripheral arterial chemoreceptors in the carotid and aortic bodies*. But during the ensuing 2 to 5 days, this inhibition fades away, allowing the respiratory center to respond with full force to the peripheral chemoreceptor stimulus from hypoxia, and ventilation increases to about five times normal.

The cause of this fading inhibition is believed to be mainly a reduction of bicarbonate ion concentration in the cerebrospinal fluid, as well as in the brain tissues. This in turn decreases the pH in the fluids surrounding the chemosensitive neurons of the respiratory center, thus increasing the respiratory stimulatory activity of the center.

An important mechanism for the gradual decrease in bicarbonate concentration is compensation by the kidneys for the respiratory alkalosis, as discussed in Chapter 30. The kidneys respond to decreased P_{CO_2} by reducing hydrogen ion secretion and increasing bicarbonate excretion. This metabolic compensation for the respiratory alkalosis gradually reduces plasma and cerebrospinal fluid bicarbonate concentration and pH toward normal and removes part of the inhibitory effect on respiration of low hydrogen ion concentration. Thus, the respiratory centers are much more responsive to the peripheral chemoreceptor stimulus caused by the hypoxia after the kidneys compensate for the alkalosis.

Increase in Red Blood Cells and Hemoglobin Concentration During Acclimatization. As discussed in Chapter 32, hypoxia is the principal stimulus for causing an increase in red blood cell production. Ordinarily, when a person remains exposed to low oxygen for weeks at a time, the hematocrit rises slowly from a normal value of 40 to 45 to an average of about 60, with an average increase in whole blood hemoglobin concentration from normal of 15 g/dl to about 20 g/dl.

In addition, the blood volume also increases, often by 20 to 30 percent, and this increase times the increased blood hemoglobin concentration gives an increase in total body hemoglobin of 50 or more percent.

Increased Diffusing Capacity After Acclimatization. The normal diffusing capacity for oxygen through the pulmonary membrane is about 21 ml/mm Hg/min, and this diffusing capacity can increase as much as threefold during exercise. A similar increase in diffusing capacity occurs at high altitude.

Part of the increase results from increased pulmonary capillary blood volume, which expands the capillaries and increases the surface area through which oxygen can diffuse into the blood. Another part results from an increase in lung air volume, which expands the surface area of the alveolar-capillary interface still more. A final part results from an increase in pulmonary arterial blood pressure; this forces blood into greater numbers of alveolar capillaries than normally—especially in the upper parts of the lungs, which are poorly perfused under usual conditions.

Peripheral Circulatory System Changes During Acclimatization—Increased Tissue Capillarity. The cardiac output often increases as much as 30 percent immediately after a person ascends to high altitude but then decreases back toward normal *over a period of weeks as the blood hematocrit increases*, so the amount of oxygen transported to the peripheral body tissues remains about normal.

Another circulatory adaptation is *growth of increased numbers of systemic circulatory capillaries* in the nonpulmonary tissues, which is called *increased tissue capillarity* (or *angiogenesis*). This occurs especially in animals born and bred at high altitudes but less so in animals that later in life become exposed to high altitude.

In active tissues exposed to chronic hypoxia, the increase in capillarity is especially marked. For instance, capillary density in right ventricular muscle increases markedly because of the combined effects of hypoxia and excess workload on the right ventricle caused by pulmonary hypertension at high altitude.

Cellular Acclimatization. In animals native to altitudes of 13,000 to 17,000 feet, cell mitochondria and cellular oxidative enzyme systems are slightly more plentiful than in sea-level inhabitants. Therefore, it is presumed that the tissue cells of high altitude–acclimatized human beings also can use oxygen more effectively than can their sea-level counterparts.

Natural Acclimatization of Native Human Beings Living at High Altitudes

Many native human beings in the Andes and in the Himalayas live at altitudes above 13,000 feet—one group in the Peruvian Andes lives at an altitude of 17,500 feet and works a mine at an altitude of 19,000 feet. Many of these natives are born at these altitudes and live there all their lives. In all aspects of acclimatization, the natives are superior to even the best-acclimatized lowlanders, even though the lowlanders might also have lived at high altitudes for 10 or more years. Acclimatization of the natives

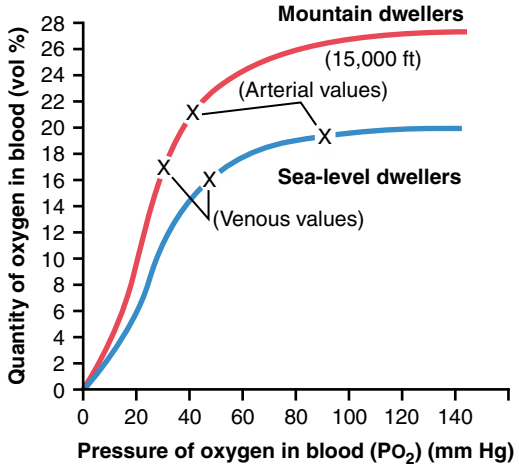


Figure 43-2 Oxygen-hemoglobin dissociation curves for blood of high-altitude residents (*red curve*) and sea-level residents (*blue curve*), showing the respective arterial and venous Po_2 levels and oxygen contents as recorded in their native surroundings. (Data from Oxygen-dissociation curves for bloods of high-altitude and sea-level residents. PAHO Scientific Publication No. 140, Life at High Altitudes, 1966.)

begins in infancy. The chest size, especially, is greatly increased, whereas the body size is somewhat decreased, giving a high ratio of ventilatory capacity to body mass. In addition, their hearts, which from birth onward pump extra amounts of cardiac output, are considerably larger than the hearts of lowlanders.

Delivery of oxygen by the blood to the tissues is also highly facilitated in these natives. For instance, Figure 43-2 shows oxygen-hemoglobin dissociation curves for natives who live at sea level and for their counterparts who live at 15,000 feet. Note that the arterial oxygen Po_2 in the natives at high altitude is only 40 mm Hg, but because of the greater quantity of hemoglobin, the quantity of oxygen in their arterial blood is greater than that in the blood of the natives at the lower altitude. Note also that the venous Po_2 in the high-altitude natives is only 15 mm Hg less than the venous Po_2 for the lowlanders, despite the very low arterial Po_2, indicating that oxygen transport to the tissues is exceedingly effective in the naturally acclimatized high-altitude natives.

Reduced Work Capacity at High Altitudes and Positive Effect of Acclimatization

In addition to the mental depression caused by hypoxia, as discussed earlier, the work capacity of all muscles is greatly decreased in hypoxia. This includes not only skeletal muscles but also cardiac muscles.

In general, work capacity is reduced in direct proportion to the decrease in maximum rate of oxygen uptake that the body can achieve.

To give an idea of the importance of acclimatization in increasing work capacity, consider the large differences in work capacities as percent of normal for unacclimatized and acclimatized people at an altitude of 17,000 feet:

	Work capacity (percent of normal)
Unacclimatized	50
Acclimatized for 2 months	68
Native living at 13,200 feet but working at 17,000 feet	87

Thus, naturally acclimatized native persons can achieve a daily work output even at high altitude almost equal to that of a lowlander at sea level, but even well-acclimatized lowlanders can almost never achieve this result.

Acute Mountain Sickness and High-Altitude Pulmonary Edema

A small percentage of people who ascend rapidly to high altitudes become acutely sick and can die if not given oxygen or removed to a low altitude. The sickness begins from a few hours up to about 2 days after ascent. Two events frequently occur:

1. *Acute cerebral edema*. This is believed to result from local vasodilation of the cerebral blood vessels, caused by the hypoxia. Dilation of the arterioles increases blood flow into the capillaries, thus increasing capillary pressure, which in turn causes fluid to leak into the cerebral tissues. The cerebral edema can then lead to severe disorientation and other effects related to cerebral dysfunction.
2. *Acute pulmonary edema*. The cause of this is still unknown, but one explanation is the following: The severe hypoxia causes the pulmonary arterioles to constrict potently, but the constriction is much greater in some parts of the lungs than in other parts, so more and more of the pulmonary blood flow is forced through fewer and fewer still unconstricted pulmonary vessels. The postulated result is that the capillary pressure in these areas of the lungs becomes especially high and local edema occurs. Extension of the process to progressively more areas of the lungs leads to spreading pulmonary edema and severe pulmonary dysfunction that can be lethal. Allowing the person to breathe oxygen usually reverses the process within hours.

Chronic Mountain Sickness

Occasionally, a person who remains at high altitude too long develops *chronic mountain sickness*, in which the following effects occur: (1) The red cell mass and hematocrit become exceptionally high, (2) the pulmonary arterial pressure becomes elevated even more than the normal elevation that occurs during acclimatization, (3) the right side of the heart becomes greatly enlarged, (4) the peripheral arterial pressure begins to fall, (5) congestive heart failure ensues, and (6) death often follows unless the person is removed to a lower altitude.

The causes of this sequence of events are probably threefold: First, the red cell mass becomes so great that the blood viscosity increases severalfold; this increased viscosity tends to *decrease* tissue blood flow so that oxygen delivery also begins to decrease. Second, the pulmonary arterioles become vasoconstricted because of the lung hypoxia. This results from the hypoxic vascular constrictor effect that normally operates to divert blood flow from low-oxygen to high-oxygen alveoli, as explained in Chapter 38. But because *all* the alveoli are now in the low-oxygen state, all the arterioles become constricted, the pulmonary arterial pressure rises excessively, and the right side of the heart fails. Third, the alveolar arteriolar spasm diverts much of the blood flow through nonalveolar pulmonary vessels, thus causing an excess of pulmonary shunt blood flow where the blood is poorly oxygenated; this further compounds the problem. Most of these people recover within days or weeks when they are moved to a lower altitude.

Effects of Acceleratory Forces on the Body in Aviation and Space Physiology

Because of rapid changes in velocity and direction of motion in airplanes or spacecraft, several types of acceleratory forces affect the body during flight. At the beginning of flight, simple linear acceleration occurs; at the end of flight, deceleration; and every time the vehicle turns, centrifugal acceleration.

Centrifugal Acceleratory Forces

When an airplane makes a turn, the force of centrifugal acceleration is determined by the following relation:

$$f = \frac{mv^2}{r}$$

in which f is centrifugal acceleratory force, m is the mass of the object, v is velocity of travel, and r is radius of curvature of the turn. From this formula, it is obvious that as the velocity increases, the *force of centrifugal acceleration increases in proportion to the square of the velocity*. It is also obvious that the force of acceleration is *directly proportional to the sharpness of the turn (the less the radius)*.

Measurement of Acceleratory Force—"G." When an aviator is simply sitting in his seat, the force with which he is pressing against the seat results from the pull of gravity and is equal to his weight. The intensity of this force is said to be +1G because it is equal to the pull of gravity. If the force with which he presses against the seat becomes five times his normal weight during pull-out from a dive, the force acting on the seat is +5 G.

If the airplane goes through an outside loop so that the person is held down by his seat belt, *negative G* is applied to his body; if the force with which he is held down by his belt is equal to the weight of his body, the negative force is −1G.

Effects of Centrifugal Acceleratory Force on the Body—(Positive G)

Effects on the Circulatory System. The most important effect of centrifugal acceleration is on the circulatory system, because blood is mobile and can be translocated by centrifugal forces.

When an aviator is subjected to *positive G*, blood is centrifuged toward the lowermost part of the body. Thus, if the centrifugal acceleratory force is +5 G and the person is in an immobilized standing position, the pressure in the veins of the feet becomes greatly increased (to about 450 mm Hg). In the sitting position, the pressure becomes nearly 300 mm Hg. And, as pressure in the vessels of the lower body increases, these vessels passively dilate so that a major portion of the blood from the upper body is translocated into the lower vessels. Because the heart cannot pump unless blood returns to it, the greater the quantity of blood "pooled" in this way in the lower body, the less that is available for the cardiac output.

Figure 43-3 shows the changes in systolic and diastolic arterial pressures (top and bottom curves, respectively) in the upper body when a centrifugal acceleratory force of +3.3 G is suddenly applied to a sitting person. Note that both these pressures fall below 22 mm Hg for the first few seconds after the acceleration begins but then return to a systolic pressure of about 55 mm Hg and a diastolic pressure of 20 mm Hg within another 10 to 15 seconds. This secondary recovery is caused mainly by activation of the baroreceptor reflexes.

Acceleration greater than 4 to 6 G causes "blackout" of vision within a few seconds and unconsciousness shortly thereafter. If this great degree of acceleration is continued, the person will die.

Effects on the Vertebrae. Extremely high acceleratory forces for even a fraction of a second can fracture the vertebrae. The degree of positive acceleration that the average person can withstand in the sitting position before vertebral fracture occurs is about 20 G.

Negative G. The effects of negative G on the body are less dramatic acutely but possibly more damaging permanently than the effects of positive G. An aviator can

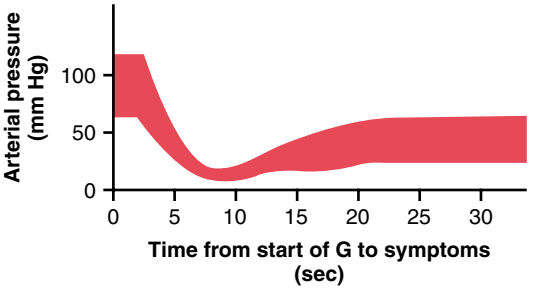


Figure 43-3 Changes in systolic (*top of curve*) and diastolic (*bottom of curve*) arterial pressures after abrupt and continuing exposure of a sitting person to an acceleratory force from top to bottom of 3.3 G. (Data from Martin EE, Henry JP: Effects of time and temperature upon tolerance to positive acceleration. J Aviation Med 22:382, 1951.)

usually go through outside loops up to negative accelerator forces of −4 to −5 G without causing permanent harm, although causing intense momentary hyperemia of the head. Occasionally, psychotic disturbances lasting for 15 to 20 minutes occur as a result of brain edema.

Occasionally, negative G forces can be so great (−20 G, for instance) and centrifugation of the blood into the head is so great that the cerebral blood pressure reaches 300 to 400 mm Hg, sometimes causing small vessels on the surface of the head and in the brain to rupture. However, the vessels inside the cranium show less tendency for rupture than would be expected for the following reason: The cerebrospinal fluid is centrifuged toward the head at the same time that blood is centrifuged toward the cranial vessels, and the greatly increased pressure of the cerebrospinal fluid acts as a cushioning buffer on the outside of the brain to prevent intracerebral vascular rupture.

Because the eyes are not protected by the cranium, intense hyperemia occurs in them during strong negative G. As a result, the eyes often become temporarily blinded with "red-out."

Protection of the Body Against Centrifugal Accelerator Forces. Specific procedures and apparatus have been developed to protect aviators against the circulatory collapse that might occur during positive G. First, if the aviator tightens his or her abdominal muscles to an extreme degree and leans forward to compress the abdomen, some of the pooling of blood in the large vessels of the abdomen can be prevented, delaying the onset of blackout. Also, special "anti-G" suits have been devised to prevent pooling of blood in the lower abdomen and legs. The simplest of these applies positive pressure to the legs and abdomen by inflating compression bags as the G increases. Theoretically, a pilot submerged in a tank or suit of water might experience little effect of G forces on the circulation because the pressures developed in the water pressing on the outside of the body during centrifugal acceleration would almost exactly balance the forces acting in the body. However, the presence of air in the lungs still allows displacement of the heart, lung tissues, and diaphragm into seriously abnormal positions despite submersion in water. Therefore, even if this procedure were used, the limit of safety almost certainly would still be less than 10 G.

Effects of Linear Acceleratory Forces on the Body

Acceleratory Forces in Space Travel. Unlike an airplane, a spacecraft cannot make rapid turns; therefore, centrifugal acceleration is of little importance except when the spacecraft goes into abnormal gyrations. However, blast-off acceleration and landing deceleration can be tremendous; both of these are types of *linear acceleration*, one positive and the other negative.

Figure 43-4 shows an approximate profile of acceleration during blast-off in a three-stage spacecraft, demonstrating that the first-stage booster causes acceleration as high as 9 G, and the second-stage booster as high as 8 G. In the standing position, the human body could not withstand this much acceleration, but in a semireclining position *transverse to the axis of acceleration*, this amount of acceleration can be withstood with ease despite the fact that the acceleratory forces continue for as long as several minutes at a time. Therefore, we see the reason for the reclining seats used by astronauts.

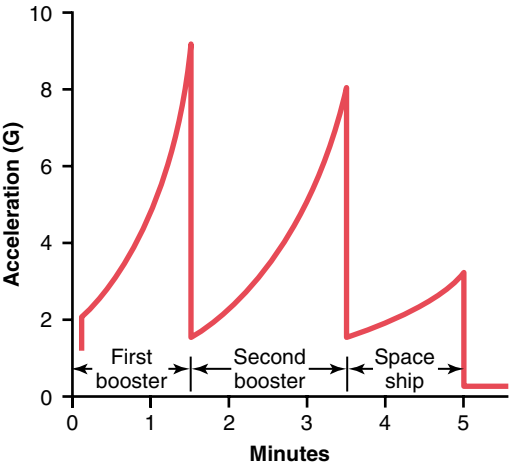


Figure 43-4 Acceleratory forces during takeoff of a spacecraft.

Problems also occur during deceleration when the spacecraft re-enters the atmosphere. A person traveling at Mach 1 (the speed of sound and of fast airplanes) can be safely decelerated in a distance of about 0.12 mile, whereas a person traveling at a speed of Mach 100 (a speed possible in interplanetary space travel) would require a distance of about 10,000 miles for safe deceleration. The principal reason for this difference is that the total amount of energy that must be dispelled during deceleration is proportional to the *square* of the velocity, which alone increases the required distance for decelerations between Mach 1 versus Mach 100 about 10,000-fold. Therefore, deceleration must be accomplished much more slowly from high velocities than is necessary at lower velocities.

Deceleratory Forces Associated with Parachute Jumps. When the parachuting aviator leaves the airplane, his velocity of fall is at first exactly 0 feet per second. However, because of the acceleratory force of gravity, within 1 second his velocity of fall is 32 feet per second (if there is no air resistance); in 2 seconds it is 64 feet per second; and so on. As the velocity of fall increases, the air resistance tending to slow the fall also increases. Finally, the deceleratory force of the air resistance exactly balances the acceleratory force of gravity, so after falling for about 12 seconds, the person will be falling at a "terminal velocity" of 109 to 119 miles per hour (175 feet per second). If the parachutist has already reached terminal velocity before opening his parachute, an "opening shock load" of up to 1200 pounds can occur on the parachute shrouds.

The usual-sized parachute slows the fall of the parachutist to about one-ninth the terminal velocity. In other words, the speed of landing is about 20 feet per second, and the force of impact against the earth is 1/81 the impact

force without a parachute. Even so, the force of impact is still great enough to cause considerable damage to the body unless the parachutist is properly trained in landing. Actually, the force of impact with the earth is about the same as that which would be experienced by jumping without a parachute from a height of about 6 feet. Unless forewarned, the parachutist will be tricked by his senses into striking the earth with extended legs, and this will result in tremendous deceleratory forces along the skeletal axis of the body, resulting in fracture of his pelvis, vertebrae, or leg. Consequently, the trained parachutist strikes the earth with knees bent but muscles taut to cushion the shock of landing.

"Artificial Climate" in the Sealed Spacecraft

Because there is no atmosphere in outer space, an artificial atmosphere and climate must be produced in a spacecraft. Most important, the oxygen concentration must remain high enough and the carbon dioxide concentration low enough to prevent suffocation. In some earlier space missions, a capsule atmosphere containing pure oxygen at about 260 mm Hg pressure was used, but in the modern space shuttle, gases about equal to those in normal air are used, with four times as much nitrogen as oxygen and a total pressure of 760 mm Hg. The presence of nitrogen in the mixture greatly diminishes the likelihood of fire and explosion. It also protects against development of local patches of lung atelectasis that often occur when breathing pure oxygen because oxygen is absorbed rapidly when small bronchi are temporarily blocked by mucous plugs.

For space travel lasting more than several months, it is impractical to carry along an adequate oxygen supply. For this reason, recycling techniques have been proposed for use of the same oxygen over and over again. Some recycling processes depend on purely physical procedures, such as electrolysis of water to release oxygen. Others depend on biological methods, such as use of algae with their large store of chlorophyll to release oxygen from carbon dioxide by the process of photosynthesis. A completely satisfactory system for recycling has yet to be achieved.

Weightlessness in Space

A person in an orbiting satellite or a nonpropelled spacecraft experiences *weightlessness*, or a state of near-zero G force, which is sometimes called *microgravity*. That is, the person is not drawn toward the bottom, sides, or top of the spacecraft but simply floats inside its chambers. The cause of this is not failure of gravity to pull on the body because gravity from any nearby heavenly body is still active. However, the gravity acts on both the spacecraft and the person at the same time so that both are pulled with exactly the same acceleratory forces and in the same direction. For this reason, the person simply is not attracted toward any specific wall of the spacecraft.

Physiologic Problems of Weightlessness (Microgravity). The physiologic problems of weightlessness have not proved to be of much significance, as long as the period of weightlessness is not too long. Most of the problems that do occur are related to three effects of the weightlessness: (1) motion sickness during the first few days of travel, (2) translocation of fluids within the body because of failure of gravity to cause normal hydrostatic pressures, and (3) diminished physical activity because no strength of muscle contraction is required to oppose the force of gravity.

Almost 50 percent of astronauts experience motion sickness, with nausea and sometimes vomiting, during the first 2 to 5 days of space travel. This probably results from an unfamiliar pattern of motion signals arriving in the equilibrium centers of the brain, and at the same time lack of gravitational signals.

The observed effects of prolonged stay in space are the following: (1) decrease in blood volume, (2) decrease in red blood cell mass, (3) decrease in muscle strength and work capacity, (4) decrease in maximum cardiac output, and (5) loss of calcium and phosphate from the bones, as well as loss of bone mass. Most of these same effects also occur in people who lie in bed for an extended period of time. For this reason, exercise programs are carried out by astronauts during prolonged space missions.

In previous space laboratory expeditions in which the exercise program had been less vigorous, the astronauts had severely decreased work capacities for the first few days after returning to earth. They also tended to faint (and still do, to some extent) when they stood up during the first day or so after return to gravity because of diminished blood volume and diminished responses of the arterial pressure control mechanisms.

Cardiovascular, Muscle, and Bone "Deconditioning" During Prolonged Exposure to Weightlessness. During very long space flights and prolonged exposure to microgravity, gradual "deconditioning" effects occur on the cardiovascular system, skeletal muscles, and bone despite rigorous exercise during the flight. Studies of astronauts on space flights lasting several months have shown that they may lose as much 1.0 percent of their bone mass each month even though they continue to exercise. Substantial atrophy of cardiac and skeletal muscles also occurs during prolonged exposure to a microgravity environment.

One of the most serious effects is cardiovascular "deconditioning," which includes decreased work capacity, reduced blood volume, impaired baroreceptor reflexes, and reduced orthostatic tolerance. These changes greatly limit the astronauts' ability to stand upright or perform normal daily activities after returning to the full gravity of Earth.

Astronauts returning from space flights lasting 4 to 6 months are also susceptible to bone fractures and may require several weeks before they return to preflight cardiovascular, bone, and muscle fitness. As space flights become longer in preparation for possible human exploration of other planets, such as Mars, the effects of prolonged microgravity could pose a very serious threat to astronauts after they land, especially in the event of an emergency landing. Therefore, considerable research effort has been directed toward developing countermeasures, in addition to exercise, that can prevent or more effectively attenuate these changes. One such countermeasure that is being tested is the application of intermittent "artificial gravity" caused by short periods (e.g., 1 hour each day) of centrifugal acceleration of the astronauts while they sit in specially designed short-arm centrifuges that create forces of up to 2 to 3 G.

Bibliography

Adams GR, Caiozzo VJ, Baldwin KM: Skeletal muscle unweighting: spaceflight and ground-based models, *J Appl Physiol* 95:2185, 2003.

Bärtsch P, Mairbäurl H, Maggiorini M, et al: Physiological aspects of high-altitude pulmonary edema, *J Appl Physiol* 98:1101, 2005.

Basnyat B, Murdoch DR: High-altitude illness, *Lancet* 361:1967, 2003.

Convertino VA: Mechanisms of microgravity induced orthostatic intolerance: implications for effective countermeasures, *J Gravit Physiol* 9:1, 2002.

Diedrich A, Paranjape SY, Robertson D: Plasma and blood volume in space, *Am J Med Sci* 334:80, 2007.

Di Rienzo M, Castiglioni P, Iellamo F, et al: Dynamic adaptation of cardiac baroreflex sensitivity to prolonged exposure to microgravity: data from a 16-day spaceflight, *J Appl Physiol* 105:1569, 2008.

Hackett PH, Roach RC: High-altitude illness, *N Engl J Med* 345:107, 2001.

Hainsworth R, Drinkhill MJ: Cardiovascular adjustments for life at high altitude, *Respir Physiol Neurobiol* 158:204, 2007.

Hoschele S, Mairbaurl H: Alveolar flooding at high altitude: failure of reabsorption? *News Physiol Sci* 18:55, 2003.

LeBlanc AD, Spector ER, Evans HJ, et al: Skeletal responses to space flight and the bed rest analog: a review, *J Musculoskelet Neuronal Interact* 7:33, 2007.

Penaloza D, Arias-Stella J: The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness, *Circulation* 115:1132, 2007.

Smith SM, Heer M: Calcium and bone metabolism during space flight, *Nutrition* 18:849, 2002.

West JB: Man in space, *News Physiol Sci* 1:198, 1986.

West JB: George I. Finch and his pioneering use of oxygen for climbing at extreme altitudes, *J Appl Physiol* 94:1702, 2003.

Physiology of Deep-Sea Diving and Other Hyperbaric Conditions

When human beings descend beneath the sea, the pressure around them increases tremendously. To keep the lungs from collapsing, air must be supplied at very high pressure to keep them inflated. This exposes the blood in the lungs to extremely high alveolar gas pressure, a condition called *hyperbarism*. Beyond certain limits, these high pressures cause tremendous alterations in body physiology and can be lethal.

Relationship of Pressure to Sea Depth. A column of seawater 33 feet (10.1 meters) deep exerts the same pressure at its bottom as the pressure of the atmosphere above the sea. Therefore, a person 33 feet beneath the ocean surface is exposed to 2 atmospheres pressure, 1 atmosphere of pressure caused by the weight of the air above the water and the second atmosphere by the weight of the water itself. At 66 feet the pressure is 3 atmospheres, and so forth, in accord with the table in Figure 44-1.

Effect of Sea Depth on the Volume of Gases—Boyle's Law. Another important effect of depth is compression of gases to smaller and smaller volumes. The lower part of Figure 44-1 shows a bell jar at sea level containing 1 liter of air. At 33 feet beneath the sea, where the pressure is 2 atmospheres, the volume has been compressed to only one-half liter, and at 8 atmospheres (233 feet) to one-eighth liter. Thus, the volume to which a given quantity of gas is compressed is inversely proportional to the pressure. This is a principle of physics called *Boyle's law*, which is extremely important in diving physiology because increased pressure can collapse the air chambers of the diver's body, especially the lungs, and often causes serious damage.

Many times in this chapter it is necessary to refer to *actual volume* versus *sea-level volume*. For instance, we might speak of an actual volume of 1 liter at a depth of 300 feet; this is the same *quantity* of air as a sea-level volume of 10 liters.

Effect of High Partial Pressures of Individual Gases on the Body

The individual gases to which a diver is exposed when breathing air are *nitrogen*, *oxygen*, and *carbon dioxide*; each of these at times can cause significant physiologic effects at high pressures.

Nitrogen Narcosis at High Nitrogen Pressures

About four fifths of the air is nitrogen. At sea-level pressure, the nitrogen has no significant effect on bodily function, but at high pressures it can cause varying degrees of narcosis. When the diver remains beneath the sea for an hour or more and is breathing compressed air, the depth at which the first symptoms of mild narcosis appear is about 120 feet. At this level the diver begins to exhibit joviality and to lose many of his or her cares. At 150 to 200 feet, the diver becomes drowsy. At 200 to 250 feet, his or her strength wanes considerably, and the diver often becomes too clumsy to perform the work required. Beyond 250 feet (8.5 atmospheres pressure), the diver usually becomes almost useless as a result of nitrogen narcosis if he or she remains at these depths too long.

Nitrogen narcosis has characteristics similar to those of alcohol intoxication, and for this reason it has frequently been called "raptures of the depths." The mechanism of the narcotic effect is believed to be the same as that of most other gas anesthetics. That is, it dissolves in the fatty substances in neuronal membranes and, because of its *physical* effect on altering ionic conductance through the membranes, reduces neuronal excitability.

Oxygen Toxicity at High Pressures

Effect of Very High P_{O_2} on Blood Oxygen Transport. When the P_{O_2} in the blood rises above 100 mm Hg, the amount of oxygen dissolved in the water of the blood increases markedly. This is shown in Figure 44-2, which depicts the same oxygen-hemoglobin dissociation curve as that shown in Chapter 40 but with the alveolar P_{O_2} extended to more than 3000 mm Hg. Also depicted by the lowest curve in the figure is the *volume of oxygen dissolved in the fluid of the blood* at each P_{O_2} level. Note that

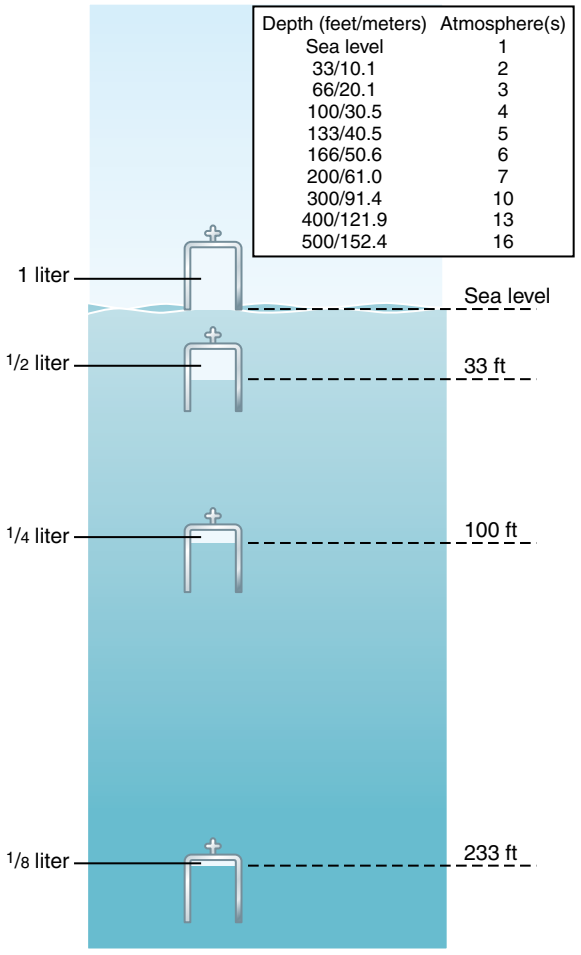


Figure 44-1 Effect of sea depth on pressure (*top table*) and on gas volume (*bottom*).

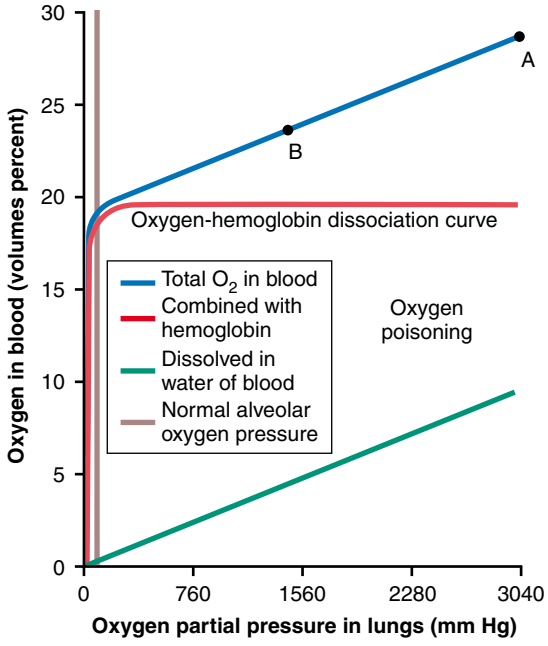


Figure 44-2 Quantity of oxygen dissolved in the fluid of the blood and in combination with hemoglobin at very high P_{O_2}s.

in the normal range of alveolar P_{O_2} (below 120 mm Hg), almost none of the total oxygen in the blood is accounted for by dissolved oxygen, but as the oxygen pressure rises into the thousands of millimeters of mercury, a large portion of the total oxygen is then dissolved in the water of the blood, in addition to that bound with hemoglobin.

Effect of High Alveolar P_{O_2} on Tissue P_{O_2}. Let us assume that the P_{O_2} in the lungs is about 3000 mm Hg (4 atmospheres pressure). Referring to Figure 44-2, one finds that this represents a total oxygen content in each 100 milliliters of blood of about 29 volumes percent, as demonstrated by point A in the figure—this means 20 volumes percent bound with hemoglobin and 9 volumes percent dissolved in the blood water. As this blood passes through the tissue capillaries and the tissues use their normal amount of oxygen, about 5 milliliters from each 100 milliliters of blood, the oxygen content on leaving the tissue capillaries is still 24 volumes percent (point B in the figure). At this point, the P_{O_2} is approximately 1200 mm Hg, which means that oxygen is delivered to the tissues at this extremely high pressure instead of at the normal value of 40 mm Hg. Thus, once the alveolar P_{O_2} rises above a critical level, the hemoglobin-oxygen buffer mechanism (discussed in Chapter 40) is no longer capable of keeping the tissue P_{O_2} in the normal, safe range between 20 and 60 mm Hg.

Acute Oxygen Poisoning. The extremely high tissue P_{O_2} that occurs when oxygen is breathed at very high alveolar oxygen pressure can be detrimental to many of the body's tissues. For instance, breathing oxygen at 4 atmospheres pressure of oxygen (P_{O_2} = 3040 mm Hg) will cause brain *seizures followed by coma* in most people within 30 to 60 minutes. The seizures often occur without warning and, for obvious reasons, are likely to be lethal to divers submerged beneath the sea.

Other symptoms encountered in acute oxygen poisoning include nausea, muscle twitchings, dizziness, disturbances of vision, irritability, and disorientation. Exercise greatly increases the diver's susceptibility to oxygen toxicity, causing symptoms to appear much earlier and with far greater severity than in the resting person.

Excessive Intracellular Oxidation as a Cause of Nervous System Oxygen Toxicity—"Oxidizing Free Radicals." Molecular oxygen (O_2) has little capability of oxidizing other chemical compounds. Instead, it must first be converted into an "active" form of oxygen. There are several forms of active oxygen called *oxygen free radicals*. One of the most important of these is the *superoxide free radical* O_2^-, and another is the *peroxide radical* in the form of *hydrogen peroxide*. Even when the tissue P_{O_2} is normal at the level of 40 mm Hg, small amounts of free radicals are continually being formed from the dissolved molecular oxygen. Fortunately, the tissues also contain multiple enzymes that rapidly remove these free radicals, including *peroxidases, catalases*, and *superoxide*

dismutases. Therefore, so long as the hemoglobin-oxygen buffering mechanism maintains a normal tissue P_{O_2}, the oxidizing free radicals are removed rapidly enough that they have little or no effect in the tissues.

Above a critical alveolar P_{O_2} (above about 2 atmospheres P_{O_2}), the hemoglobin-oxygen buffering mechanism fails, and the tissue P_{O_2} can then rise to hundreds or thousands of millimeters of mercury. At these high levels, the amounts of oxidizing free radicals literally swamp the enzyme systems designed to remove them, and now they can have serious destructive and even lethal effects on the cells. One of the principal effects is to oxidize the polyunsaturated fatty acids that are essential components of many of the cell membranes. Another effect is to oxidize some of the cellular enzymes, thus damaging severely the cellular metabolic systems. The nervous tissues are especially susceptible because of their high lipid content. Therefore, most of the acute lethal effects of acute oxygen toxicity are caused by brain dysfunction.

Chronic Oxygen Poisoning Causes Pulmonary Disability. A person can be exposed to only 1 atmosphere pressure of oxygen almost indefinitely without developing the *acute* oxygen toxicity of the nervous system just described. However, after only about 12 hours of 1 atmosphere oxygen exposure, *lung passageway congestion, pulmonary edema*, and *atelectasis* caused by damage to the linings of the bronchi and alveoli begin to develop. The reason for this effect in the lungs but not in other tissues is that the air spaces of the lungs are directly exposed to the high oxygen pressure, but oxygen is delivered to the other body tissues at almost normal P_{O_2} because of the hemoglobin-oxygen buffer system.

Carbon Dioxide Toxicity at Great Depths in the Sea

If the diving gear is properly designed and functions properly, the diver has no problem due to carbon dioxide toxicity because depth alone does not increase the carbon dioxide partial pressure in the alveoli. This is true because depth does not increase the rate of carbon dioxide production in the body, and as long as the diver continues to breathe a normal tidal volume and expires the carbon dioxide as it is formed, alveolar carbon dioxide pressure will be maintained at a normal value.

In certain types of diving gear, however, such as the diving helmet and some types of rebreathing apparatuses, carbon dioxide can build up in the dead space air of the apparatus and be rebreathed by the diver. Up to an alveolar carbon dioxide pressure (P_{CO_2}) of about 80 mm Hg, twice that in normal alveoli, the diver usually tolerates this buildup by increasing the minute respiratory volume a maximum of 8- to 11-fold to compensate for the increased carbon dioxide. Beyond 80 mm Hg alveolar P_{CO_2}, the situation becomes intolerable, and eventually the respiratory center begins to be depressed, rather than excited, because of the negative tissue metabolic effects of high P_{CO_2}. The diver's respiration then begins to fail rather than to compensate. In addition, the diver develops severe respiratory acidosis and varying degrees of lethargy, narcosis, and finally even anesthesia, as discussed in Chapter 42.

Decompression of the Diver After Excess Exposure to High Pressure

When a person breathes air under high pressure for a long time, the amount of nitrogen dissolved in the body fluids increases. The reason for this is the following: Blood flowing through the pulmonary capillaries becomes saturated with nitrogen to the same high pressure as that in the alveolar breathing mixture. And over several more hours, enough nitrogen is carried to all the tissues of the body to raise their tissue P_{n_2} also to equal the P_{n_2} in the breathing air.

Because nitrogen is not metabolized by the body, it remains dissolved in all the body tissues until the nitrogen pressure in the lungs is decreased back to some lower level, at which time the nitrogen can be removed by the reverse respiratory process; however, this removal often takes hours to occur and is the source of multiple problems collectively called *decompression sickness*.

Volume of Nitrogen Dissolved in the Body Fluids at Different Depths. At sea level, almost exactly 1 liter of nitrogen is dissolved in the entire body. Slightly less than one half of this is dissolved in the water of the body and a little more than one half in the fat of the body. This is true because nitrogen is five times as soluble in fat as in water.

After the diver has become saturated with nitrogen, the *sea-level volume of nitrogen* dissolved in the body at different depths is as follows:

Feet	Liters
0	1
33	2
100	4
200	7
300	10

Several hours are required for the gas pressures of nitrogen in all the body tissues to come nearly to equilibrium with the gas pressure of nitrogen in the alveoli. The reason for this is that the blood does not flow rapidly enough and the nitrogen does not diffuse rapidly enough to cause instantaneous equilibrium. The nitrogen dissolved in the water of the body comes to almost complete equilibrium in less than 1 hour, but the fat tissue, requiring five times as much transport of nitrogen and having a relatively poor blood supply, reaches equilibrium only after several hours. For this reason, if a person remains at deep levels for only a few minutes, not much nitrogen dissolves in the body fluids and tissues, whereas if the person remains at a deep level for several hours, both the body water and body fat become saturated with nitrogen.

Decompression Sickness (Synonyms: Bends, Compressed Air Sickness, Caisson Disease, Diver's Paralysis, Dysbarism). If a diver has been beneath the sea long enough that large amounts of nitrogen have dissolved in his or her body and the diver then suddenly comes back to the surface of the sea, significant quantities of nitrogen bubbles can develop in the body fluids either intracellularly or extracellularly and can cause minor or serious damage in almost any area of the body, depending on the number and sizes of bubbles formed; this is called *decompression sickness*.

The principles underlying bubble formation are shown in Figure 44-3. In Figure 44-3*A*, the diver's tissues have become equilibrated to a high *dissolved nitrogen pressure* (Pn_2 = 3918 mm Hg), about 6.5 times the normal amount of nitrogen in the tissues. As long as the diver remains deep beneath the sea, the pressure against the outside of his or her body (5000 mm Hg) compresses all the body tissues sufficiently to keep the excess nitrogen gas dissolved. But when the diver suddenly rises to sea level (Figure 44-3*B*), the pressure on the outside of the body becomes only 1 atmosphere (760 mm Hg), while the gas pressure inside the body fluids is the sum of the pressures of water vapor, carbon dioxide, oxygen, and nitrogen, or a total of 4065 mm Hg, 97 percent of which is caused by the nitrogen. Obviously, this total value of 4065 mm Hg is far greater than the 760 mm Hg pressure on the outside of the body. Therefore, the gases can escape from the dissolved state and form actual bubbles, composed almost entirely of nitrogen, both in the tissues and in the blood where they plug many small blood vessels. The bubbles may not appear for many minutes to hours because sometimes the gases can remain dissolved in the "supersaturated" state for hours before bubbling.

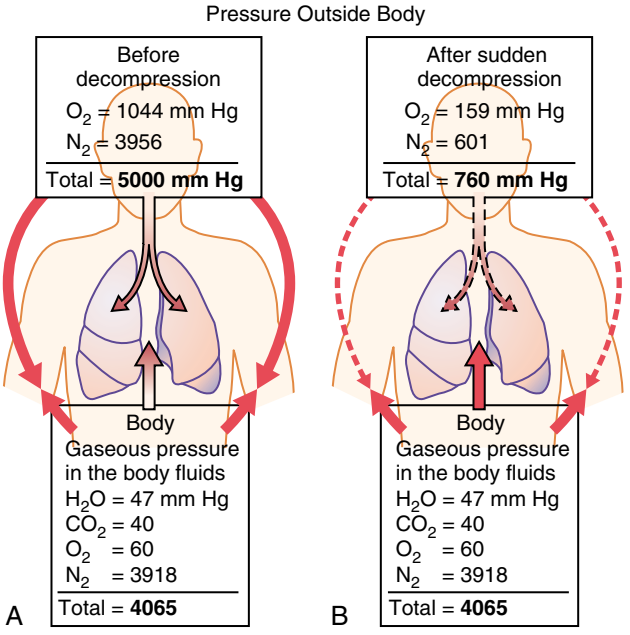


Figure 44-3 Gaseous pressures both inside and outside the body, showing (*A*) saturation of the body to high gas pressures when breathing air at a total pressure of 5000 mm Hg, and (*B*) the great excesses of intrabody pressures that are responsible for bubble formation in the tissues when the lung intra-alveolar pressure body is suddenly returned from 5000 mm Hg to normal pressure of 760 mm Hg.

Symptoms of Decompression Sickness ("Bends"). The symptoms of decompression sickness are caused by gas bubbles blocking many blood vessels in different tissues. At first, only the smallest vessels are blocked by minute bubbles, but as the bubbles coalesce, progressively larger vessels are affected. Tissue ischemia and sometimes tissue death result.

In most people with decompression sickness, the symptoms are pain in the joints and muscles of the legs and arms, affecting 85 to 90 percent of those persons who develop decompression sickness. The joint pain accounts for the term "bends" that is often applied to this condition.

In 5 to 10 percent of people with decompression sickness, nervous system symptoms occur, ranging from dizziness in about 5 percent to paralysis or collapse and unconsciousness in as many as 3 percent. The paralysis may be temporary, but in some instances, damage is permanent.

Finally, about 2 percent of people with decompression sickness develop "the chokes," caused by massive numbers of microbubbles plugging the capillaries of the lungs; this is characterized by serious shortness of breath, often followed by severe pulmonary edema and, occasionally, death.

Nitrogen Elimination from the Body; Decompression Tables. If a diver is brought to the surface slowly, enough of the dissolved nitrogen can usually be eliminated by expiration through the lungs to prevent decompression sickness. About two thirds of the total nitrogen is liberated in 1 hour and about 90 percent in 6 hours.

Decompression tables that detail procedures for safe decompression have been prepared by the U.S. Navy. To give the student an idea of the decompression process, a diver who has been breathing air and has been on the sea bottom for 60 minutes at a depth of 190 feet is decompressed according to the following schedule:

10 minutes at 50 feet depth
17 minutes at 40 feet depth
19 minutes at 30 feet depth
50 minutes at 20 feet depth
84 minutes at 10 feet depth

Thus, for a work period on the bottom of only 1 hour, the total time for decompression is about 3 hours.

Tank Decompression and Treatment of Decompression Sickness. Another procedure widely used for decompression of professional divers is to put the diver into a pressurized tank and then to lower the pressure gradually back to normal atmospheric pressure, using essentially the same time schedule as noted earlier.

Tank decompression is even more important for treating people in whom symptoms of decompression sickness develop minutes or even hours after they have returned to the surface. In this case, the diver is recompressed immediately to a deep level. Then decompression is carried out over a period several times as long as the usual decompression period.

"Saturation Diving" and Use of Helium-Oxygen Mixtures in Deep Dives. When divers must work at very deep levels—between 250 feet and nearly 1000 feet—they frequently live in a large compression tank for days or weeks at a time, remaining compressed at a pressure level near that at which they will be working. This keeps the tissues and fluids of the body saturated with the gases to which they will be exposed while diving. Then, when they return to the same tank after working, there are no significant changes in pressure, so decompression bubbles do not occur.

In very deep dives, especially during saturation diving, helium is usually used in the gas mixture instead of nitrogen for three reasons: (1) it has only about one-fifth the narcotic effect of nitrogen; (2) only about one half as much volume of helium dissolves in the body tissues as nitrogen, and the volume that does dissolve diffuses out of the tissues during decompression several times as rapidly as does nitrogen, thus reducing the problem of decompression sickness; and (3) the low density of helium (one seventh the density of nitrogen) keeps the airway resistance for breathing at a minimum, which is very important because highly compressed nitrogen is so dense that airway resistance can become extreme, sometimes making the work of breathing beyond endurance.

Finally, in very deep dives it is important to reduce the oxygen concentration in the gaseous mixture because otherwise oxygen toxicity would result. For instance, at a depth of 700 feet (22 atmospheres of pressure), a 1 percent oxygen mixture will provide all the oxygen required by the diver, whereas a 21 percent mixture of oxygen (the percentage in air) delivers a P_{O_2} to the lungs of more than 4 atmospheres, a level very likely to cause seizures in as little as 30 minutes.

Scuba (Self-Contained Underwater Breathing Apparatus) Diving

Before the 1940s, almost all diving was done using a diving helmet connected to a hose through which air was pumped to the diver from the surface. Then, in 1943, French explorer Jacques Cousteau popularized a *self-contained underwater breathing apparatus*, known as the SCUBA apparatus. The type of SCUBA apparatus used in more than 99 percent of all sports and commercial diving is the *open-circuit demand system* shown in Figure 44-4. This system consists of the following components: (1) one or more tanks of compressed air or some other breathing mixture, (2) a first-stage "reducing" valve for reducing the very high pressure from the tanks to a low pressure level, (3) a combination inhalation "demand" valve and exhalation valve that allows air to be pulled into the lungs with slight negative pressure of breathing and then to be exhaled into the sea at a pressure level slightly positive to the surrounding water pressure, and (4) a mask and tube system with small "dead space."

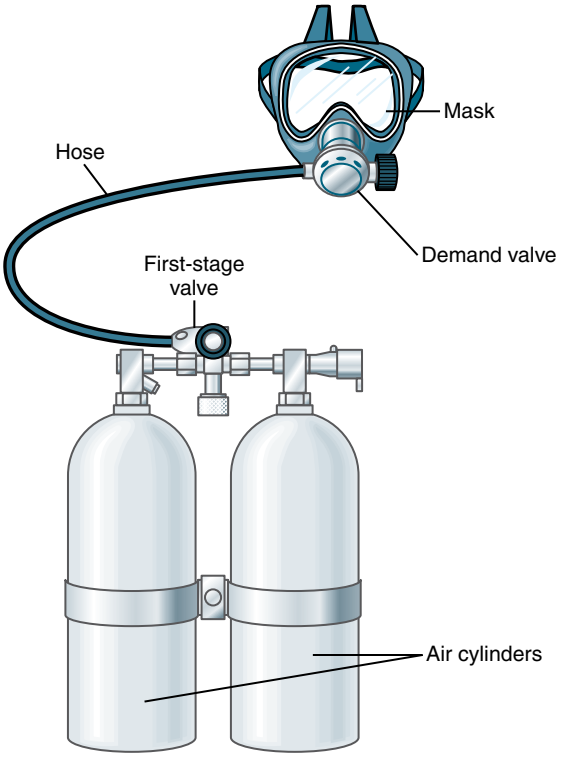


Figure 44-4 Open-circuit demand type of SCUBA apparatus.

The demand system operates as follows: The first-stage reducing valve reduces the pressure from the tanks so that the air delivered to the mask has a pressure only a few mm Hg greater than the surrounding water pressure. The breathing mixture does not flow continually into the mask. Instead, with each inspiration, slight extra negative pressure in the demand valve of the mask pulls the diaphragm of the valve open, and this automatically releases air from the tank into the mask and lungs. In this way, only the amount of air needed for inhalation enters the mask. Then, on expiration, the air cannot go back into the tank but instead is expired into the sea.

The most important problem in use of the self-contained underwater breathing apparatus is the limited amount of time one can remain beneath the sea surface; for instance, only a few minutes are possible at a 200-foot depth. The reason for this is that tremendous airflow from the tanks is required to wash carbon dioxide out of the lungs—the greater the depth, the greater the airflow in terms of *quantity* of air per minute that is required, because the *volumes* have been compressed to small sizes.

Special Physiologic Problems in Submarines

Escape from Submarines. Essentially the same problems encountered in deep-sea diving are often met in relation to submarines, especially when it is necessary to escape from a submerged submarine. Escape is possible from as deep as 300 feet without using any apparatus. However, proper use of rebreathing devices, especially when using helium, theoretically can allow escape from as deep as 600 feet or perhaps more.

One of the major problems of escape is prevention of air embolism. As the person ascends, the gases in the lungs expand and sometimes rupture a pulmonary blood vessel, forcing the gases to enter the vessel and cause air embolism of the circulation. Therefore, as the person ascends, he or she must make a special effort to exhale continually.

Health Problems in the Submarine Internal Environment. Except for escape, submarine medicine generally centers on several engineering problems to keep hazards out of the internal environment. First, in atomic submarines, there exists the problem of radiation hazards, but with appropriate shielding, the amount of radiation received by the crew submerged beneath the sea has been less than normal radiation received above the surface of the sea from cosmic rays.

Second, poisonous gases on occasion escape into the atmosphere of the submarine and must be controlled rapidly. For instance, during several weeks' submergence, cigarette smoking by the crew can liberate enough carbon monoxide, if not removed rapidly, to cause carbon monoxide poisoning. And, on occasion, even Freon gas has been found to diffuse out of refrigeration systems in sufficient quantity to cause toxicity.

Hyperbaric Oxygen Therapy

The intense oxidizing properties of high-pressure oxygen (*hyperbaric oxygen*) can have valuable therapeutic effects in several important clinical conditions. Therefore, large pressure tanks are now available in many medical centers into which patients can be placed and treated with hyperbaric oxygen. The oxygen is usually administered at Po_2s of 2 to 3 atmospheres of pressure through a mask or intratracheal tube, whereas the gas around the body is normal air compressed to the same high-pressure level.

It is believed that the same oxidizing free radicals responsible for oxygen toxicity are also responsible for at least some of the therapeutic benefits. Some of the conditions in which hyperbaric oxygen therapy has been especially beneficial follow.

Probably the most successful use of hyperbaric oxygen has been for treatment of *gas gangrene*. The bacteria that cause this condition, *clostridial organisms*, grow best under anaerobic conditions and stop growing at oxygen pressures greater than about 70 mm Hg. Therefore, hyperbaric oxygenation of the tissues can frequently stop the infectious process entirely and thus convert a condition that formerly was almost 100 percent fatal into one that is cured in most instances by early treatment with hyperbaric therapy.

Other conditions in which hyperbaric oxygen therapy has been either valuable or possibly valuable include decompression sickness, arterial gas embolism, carbon monoxide poisoning, osteomyelitis, and myocardial infarction.

Bibliography

Butler PJ: Diving beyond the limits, *News Physiol Sci* 16:222, 2001.

Leach RM, Rees PJ, Wilmshurst P: Hyperbaric oxygen therapy, *BMJ* 317:1140, 1998.

Lindholm P, Lundgren CE: The physiology and pathophysiology of human breath-hold diving, *J Appl Physiol* 106:284, 2009.

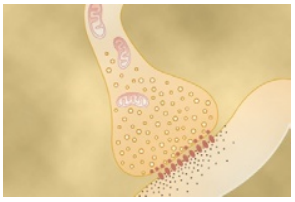
Moon RE, Cherry AD, Stolp BW, et al: Pulmonary Gas Exchange in Diving, *J Appl Physiol* 2008 [Epub ahead of print].

Neuman TS: Arterial gas embolism and decompression sickness, *News Physiol Sci* 17:77, 2002.

Pendergast DR, Lundgren CEG: The physiology and pathophysiology of the hyperbaric and diving environments, *J Appl Physiol* 106:274, 2009.

Thom SR: Oxidative stress is fundamental to hyperbaric oxygen therapy, *J Appl Physiol* 2008 doi:10.1152/japplphysiol.91004.

Organization of the Nervous System, Basic Functions of Synapses, and Neurotransmitters



The nervous system is unique in the vast complexity of thought processes and control actions it can perform. It receives each minute literally millions of bits of information from the different sensory nerves and sensory organs and then integrates all these to determine responses to be made by the body.

Before beginning this discussion of the nervous system, the reader should review Chapters 5 and 7, which present the principles of membrane potentials and transmission of signals in nerves and through neuromuscular junctions.

General Design of the Nervous System

Central Nervous System Neuron: The Basic Functional Unit

The central nervous system contains more than 100 billion neurons. Figure 45-1 shows a typical neuron of a type found in the brain motor cortex. Incoming signals enter this neuron through synapses located mostly on the neuronal dendrites, but also on the cell body. For different types of neurons, there may be only a few hundred or as many as 200,000 such synaptic connections from input fibers. Conversely, the output signal travels by way of a single axon leaving the neuron. Then, this axon has many separate branches to other parts of the nervous system or peripheral body.

A special feature of most synapses is that the signal normally passes only in the forward direction, from the axon of a preceding neuron to dendrites on cell membranes of subsequent neurons. This forces the signal to travel in required directions for performing specific nervous functions.

Sensory Part of the Nervous System—Sensory Receptors

Most activities of the nervous system are initiated by sensory experiences that excite *sensory receptors,* whether visual receptors in the eyes, auditory receptors in the ears, tactile receptors on the surface of the body, or other kinds of receptors. These sensory experiences can either cause immediate reactions from the brain, or memories of the experiences can be stored in the brain for minutes, weeks, or years and determine bodily reactions at some future date.

Figure 45-2 shows the *somatic* portion of the sensory system, which transmits sensory information from the receptors of the entire body surface and from some deep structures. This information enters the central nervous system through peripheral nerves and is conducted immediately to multiple sensory areas in (1) the spinal cord at all levels; (2) the reticular substance of the medulla, pons, and mesencephalon of the brain; (3) the cerebellum; (4) the thalamus; and (5) areas of the cerebral cortex.

Motor Part of the Nervous System—Effectors

The most important eventual role of the nervous system is to control the various bodily activities. This is achieved by controlling (1) contraction of appropriate skeletal muscles throughout the body, (2) contraction of smooth muscle in the internal organs, and (3) secretion of active chemical substances by both exocrine and endocrine glands in many parts of the body. These activities are collectively called *motor functions* of the nervous system, and the muscles and glands are called *effectors* because they are the actual anatomical structures that perform the functions dictated by the nerve signals.

Figure 45-3 shows the *"skeletal" motor nerve axis* of the nervous system for controlling skeletal muscle contraction. Operating parallel to this axis is another system, called the *autonomic nervous system,* for controlling smooth muscles, glands, and other internal bodily systems; this is discussed in Chapter 60.

Note in Figure 45-3 that the skeletal muscles can be controlled from many levels of the central nervous system, including (1) the spinal cord; (2) the reticular substance of the medulla, pons, and mesencephalon; (3) the basal ganglia; (4) the cerebellum; and (5) the motor cortex. Each of these areas plays its own specific role, the lower regions concerned primarily with automatic, instantaneous muscle responses to sensory stimuli, and the higher regions

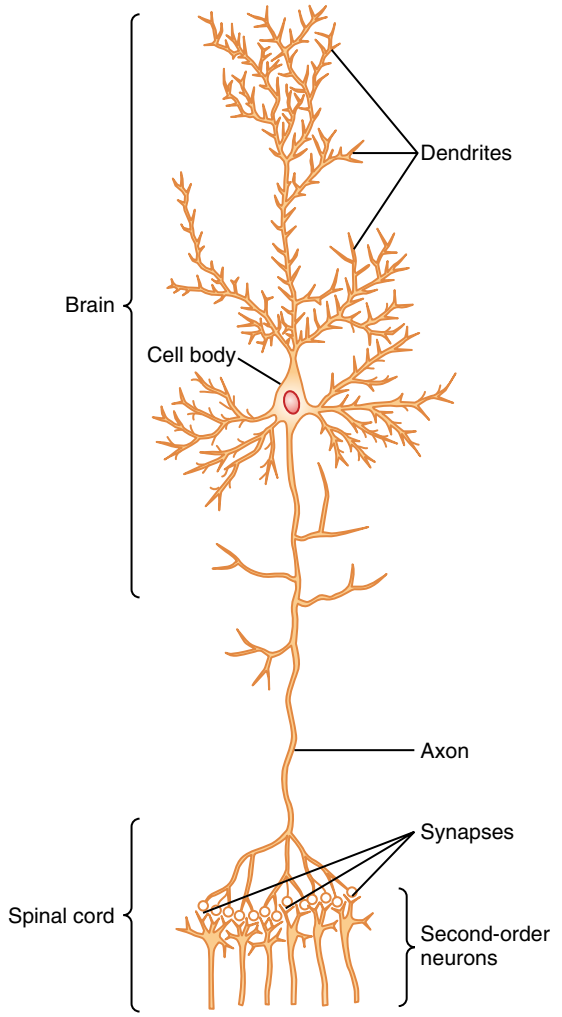


Figure 45-1 Structure of a large neuron in the brain, showing its important functional parts. (Redrawn from Guyton AC: Basic Neuroscience: Anatomy and Physiology. Philadelphia: WB Saunders, 1987.)

with deliberate complex muscle movements controlled by the thought processes of the brain.

Processing of Information—"Integrative" Function of the Nervous System

One of the most important functions of the nervous system is to process incoming information in such a way that *appropriate* mental and motor responses will occur. More than 99 percent of all sensory information is discarded by the brain as irrelevant and unimportant. For instance, one is ordinarily unaware of the parts of the body that are in contact with clothing, as well as of the seat pressure when sitting. Likewise, attention is drawn only to an occasional object in one's field of vision, and even the perpetual noise of our surroundings is usually relegated to the subconscious.

But, when important sensory information excites the mind, it is immediately channeled into proper integrative and motor regions of the brain to cause desired responses. This channeling and processing of information is called the *integrative function* of the nervous system. Thus,

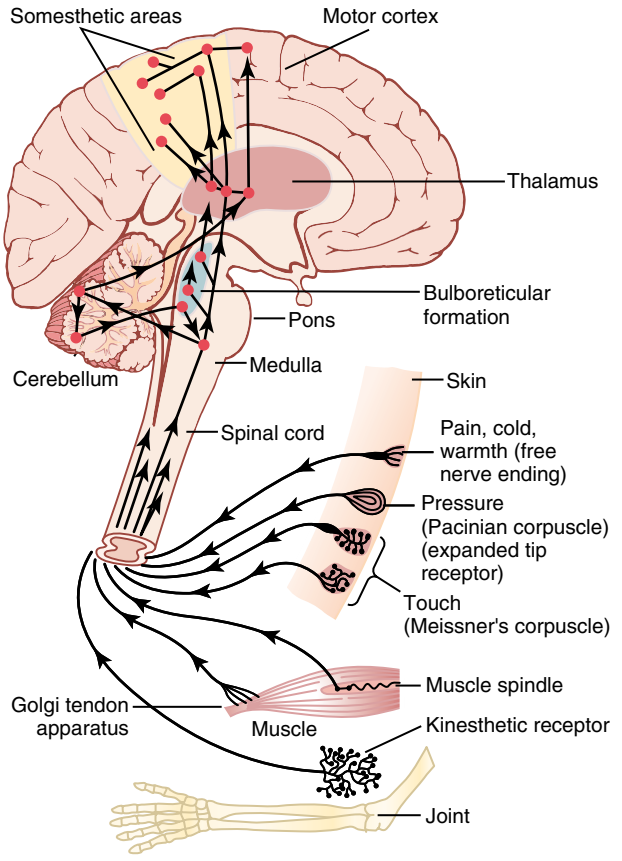


Figure 45-2 Somatosensory axis of the nervous system.

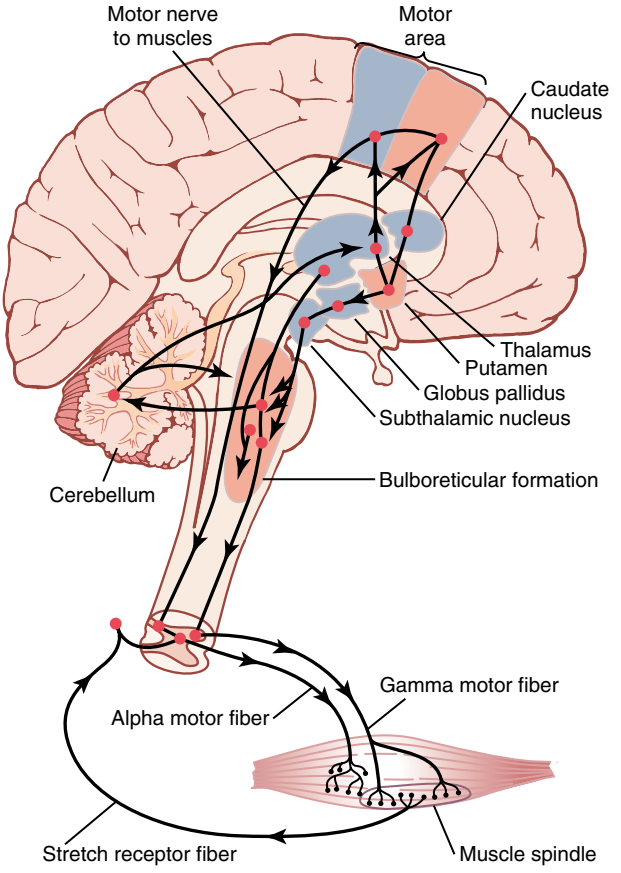


Figure 45-3 Skeletal motor nerve axis of the nervous system.

if a person places a hand on a hot stove, the desired instantaneous response is to lift the hand. And other associated responses follow, such as moving the entire body away from the stove and perhaps even shouting with pain.

Role of Synapses in Processing Information. The synapse is the junction point from one neuron to the next. Later in this chapter, we discuss the details of synaptic function. However, it is important to point out here that synapses determine the directions that the nervous signals will spread through the nervous system. Some synapses transmit signals from one neuron to the next with ease, whereas others transmit signals only with difficulty. Also, *facilitatory* and *inhibitory* signals from other areas in the nervous system can control synaptic transmission, sometimes opening the synapses for transmission and at other times closing them. In addition, some postsynaptic neurons respond with large numbers of output impulses, and others respond with only a few. Thus, the synapses perform a selective action, often blocking weak signals while allowing strong signals to pass, but at other times selecting and amplifying certain weak signals, and often channeling these signals in many directions rather than in only one direction.

Storage of Information—Memory

Only a small fraction of even the most important sensory information usually causes immediate motor response. But much of the information is stored for future control of motor activities and for use in the thinking processes. Most storage occurs in the *cerebral cortex,* but even the basal regions of the brain and the spinal cord can store small amounts of information.

The storage of information is the process we call *memory,* and this, too, is a function of the synapses. Each time certain types of sensory signals pass through sequences of synapses, these synapses become more capable of transmitting the same type of signal the next time, a process called *facilitation.* After the sensory signals have passed through the synapses a large number of times, the synapses become so facilitated that signals generated within the brain itself can also cause transmission of impulses through the same sequences of synapses, even when the sensory input is not excited. This gives the person a perception of experiencing the original sensations, although the perceptions are only memories of the sensations.

The precise mechanisms by which long-term facilitation of synapses occurs in the memory process are still uncertain, but what is known about this and other details of the sensory memory process is discussed in Chapter 57.

Once memories have been stored in the nervous system, they become part of the brain processing mechanism for future "thinking." That is, the thinking processes of the brain compare new sensory experiences with stored memories; the memories then help to select the important new sensory information and to channel this into appropriate memory storage areas for future use or into motor areas to cause immediate bodily responses.

Major Levels of Central Nervous System Function

The human nervous system has inherited special functional capabilities from each stage of human evolutionary development. From this heritage, three major levels of the central nervous system have specific functional characteristics: (1) the *spinal cord level,* (2) the *lower brain* or *subcortical level,* and (3) the *higher brain* or *cortical level.*

Spinal Cord Level

We often think of the spinal cord as being only a conduit for signals from the periphery of the body to the brain, or in the opposite direction from the brain back to the body. This is far from the truth. Even after the spinal cord has been cut in the high neck region, many highly organized spinal cord functions still occur. For instance, neuronal circuits in the cord can cause (1) walking movements, (2) reflexes that withdraw portions of the body from painful objects, (3) reflexes that stiffen the legs to support the body against gravity, and (4) reflexes that control local blood vessels, gastrointestinal movements, or urinary excretion. In fact, the upper levels of the nervous system often operate not by sending signals directly to the periphery of the body but by sending signals to the control centers of the cord, simply "commanding" the cord centers to perform their functions.

Lower Brain or Subcortical Level

Many, if not most, of what we call subconscious activities of the body are controlled in the lower areas of the brain—in the medulla, pons, mesencephalon, hypothalamus, thalamus, cerebellum, and basal ganglia. For instance, subconscious control of arterial pressure and respiration is achieved mainly in the medulla and pons. Control of equilibrium is a combined function of the older portions of the cerebellum and the reticular substance of the medulla, pons, and mesencephalon. Feeding reflexes, such as salivation and licking of the lips in response to the taste of food, are controlled by areas in the medulla, pons, mesencephalon, amygdala, and hypothalamus. And many emotional patterns, such as anger, excitement, sexual response, reaction to pain, and reaction to pleasure, can still occur after destruction of much of the cerebral cortex.

Higher Brain or Cortical Level

After the preceding account of the many nervous system functions that occur at the cord and lower brain levels, one may ask, what is left for the cerebral cortex to do? The answer to this is complex, but it begins with the fact that the cerebral cortex is an extremely large memory storehouse. The cortex never functions alone but always in association with lower centers of the nervous system.

Without the cerebral cortex, the functions of the lower brain centers are often imprecise. The vast storehouse of

cortical information usually converts these functions to determinative and precise operations.

Finally, the cerebral cortex is essential for most of our thought processes, but it cannot function by itself. In fact, it is the lower brain centers, not the cortex, that initiate *wakefulness* in the cerebral cortex, thus opening its bank of memories to the thinking machinery of the brain. Thus, each portion of the nervous system performs specific functions. But it is the cortex that opens a world of stored information for use by the mind.

Comparison of the Nervous System with a Computer

When computers were first developed, it soon became apparent that these machines have many features in common with the nervous system. First, all computers have input circuits that are comparable to the sensory portion of the nervous system, as well as output circuits that are comparable to the motor portion of the nervous system.

In simple computers, the output signals are controlled directly by the input signals, operating in a manner similar to that of simple reflexes of the spinal cord. In more complex computers, the output is determined both by input signals and by information that has already been stored in memory in the computer, which is analogous to the more complex reflex and processing mechanisms of our higher nervous system. Furthermore, as computers become even more complex, it is necessary to add still another unit, called the *central processing unit,* which determines the sequence of all operations. This unit is analogous to the control mechanisms in our brain that direct our attention first to one thought or sensation or motor activity, then to another, and so forth, until complex sequences of thought or action take place.

Figure 45-4 is a simple block diagram of a computer. Even a rapid study of this diagram demonstrates its similarity to the nervous system. The fact that the basic components of the general-purpose computer are analogous to those of the human nervous system demonstrates that the brain is basically a computer that continuously collects sensory information and uses this along with stored information to compute the daily course of bodily activity.

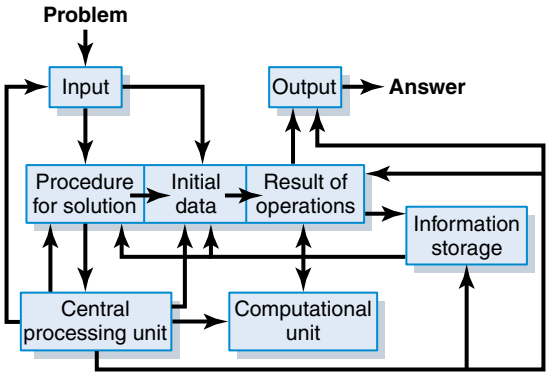


Figure 45-4 Block diagram of a general-purpose computer, showing the basic components and their interrelations.

Central Nervous System Synapses

Information is transmitted in the central nervous system mainly in the form of nerve action potentials, called simply "nerve impulses," through a succession of neurons, one after another. However, in addition, each impulse (1) may be blocked in its transmission from one neuron to the next, (2) may be changed from a single impulse into repetitive impulses, or (3) may be integrated with impulses from other neurons to cause highly intricate patterns of impulses in successive neurons. All these functions can be classified as *synaptic functions of neurons.*

Types of Synapses—Chemical and Electrical

There are two major types of synapses: (1) the *chemical synapse* and (2) the *electrical synapse.*

Almost all the synapses used for signal transmission in the central nervous system of the human being are *chemical synapses.* In these, the first neuron secretes at its nerve ending synapse a chemical substance called a *neurotransmitter* (or often called simply *transmitter substance*), and this transmitter in turn acts on receptor proteins in the membrane of the next neuron to excite the neuron, inhibit it, or modify its sensitivity in some other way. More than 40 important transmitter substances have been discovered thus far. Some of the best known are acetylcholine, norepinephrine, epinephrine, histamine, gamma-aminobutyric acid (GABA), glycine, serotonin, and glutamate.

Electrical synapses, in contrast, are characterized by direct open fluid channels that conduct electricity from one cell to the next. Most of these consist of small protein tubular structures called *gap junctions* that allow free movement of ions from the interior of one cell to the interior of the next. Such junctions were discussed in Chapter 4. Only a few examples of gap junctions have been found in the central nervous system. However, it is by way of gap junctions and other similar junctions that action potentials are transmitted from one smooth muscle fiber to the next in visceral smooth muscle (Chapter 8) and from one cardiac muscle cell to the next in cardiac muscle (Chapter 10).

"One-Way" Conduction at Chemical Synapses. Chemical synapses have one exceedingly important characteristic that makes them highly desirable for transmitting most nervous system signals. They always transmit the signals in one direction: that is, from the neuron that secretes the transmitter substance, called the *presynaptic neuron*, to the neuron on which the transmitter acts, called the *postsynaptic neuron*. This is the *principle of one-way conduction* at chemical synapses, and it is quite different from conduction through electrical synapses, which often transmit signals in either direction.

Think for a moment about the extreme importance of the one-way conduction mechanism. It allows signals to be directed toward specific goals. Indeed, it is this specific transmission of signals to discrete and highly focused areas both within the nervous system and at the terminals of the peripheral nerves that allows the nervous system to perform its myriad functions of sensation, motor control, memory, and many others.

Physiologic Anatomy of the Synapse

Figure 45-5 shows a typical *anterior motor neuron* in the anterior horn of the spinal cord. It is composed of three major parts: the *soma,* which is the main body of the neuron; a single *axon,* which extends from the soma into a peripheral nerve that leaves the spinal cord; and the *dendrites,* which are great numbers of branching projections of the soma that extend as much as 1 millimeter into the surrounding areas of the cord.

As many as 10,000 to 200,000 minute synaptic knobs called *presynaptic terminals* lie on the surfaces of the dendrites and soma of the motor neuron, about 80 to 95 percent of them on the dendrites and only 5 to 20 percent on the soma. These presynaptic terminals are the ends of nerve fibrils that originate from many other neurons. Many of these presynaptic terminals are *excitatory*—that is, they secrete a transmitter substance that excites the postsynaptic neuron. But other presynaptic terminals are *inhibitory*—they secrete a transmitter substance that inhibits the postsynaptic neuron.

Neurons in other parts of the cord and brain differ from the anterior motor neuron in (1) the size of the cell body; (2) the length, size, and number of dendrites, ranging in length from almost zero to many centimeters; (3) the length and size of the axon; and (4) the number of presynaptic terminals, which may range from only a few to as many as 200,000. These differences make neurons in different parts of the nervous system react differently to incoming synaptic signals and, therefore, perform many different functions.

Presynaptic Terminals. Electron microscopic studies of the presynaptic terminals show that they have varied anatomical forms, but most resemble small round or oval knobs and, therefore, are sometimes called *terminal knobs*, *boutons, end-feet,* or *synaptic knobs.*

Figure 45-6 illustrates the basic structure of a synapse, showing a single presynaptic terminal on the membrane surface of a postsynaptic neuron. The presynaptic terminal is separated from the postsynaptic neuronal soma by a *synaptic cleft* having a width usually of 200 to 300 angstroms. The terminal has two internal structures important to the excitatory or inhibitory function of the synapse: the *transmitter vesicles* and the *mitochondria.* The transmitter vesicles contain the *transmitter substance* that, when released into the synaptic cleft, either *excites* or *inhibits* the postsynaptic neuron—excites if the neuronal membrane contains *excitatory receptors*, inhibits if the membrane contains *inhibitory receptors.* The mitochondria provide adenosine triphosphate (ATP), which in turn supplies the energy for synthesizing new transmitter substance.

When an action potential spreads over a presynaptic terminal, depolarization of its membrane causes a small number of vesicles to empty into the cleft. The released

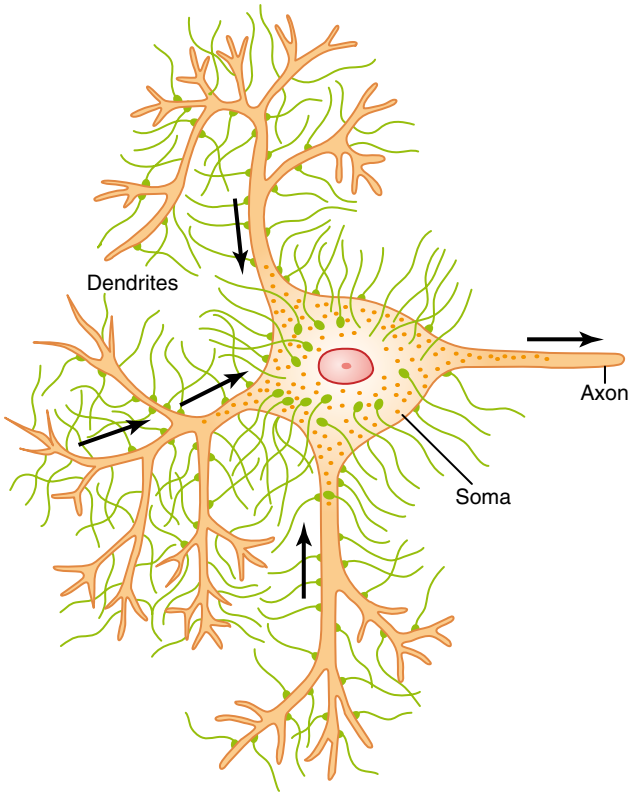


Figure 45-5 Typical anterior motor neuron, showing presynaptic terminals on the neuronal soma and dendrites. Note also the single axon.

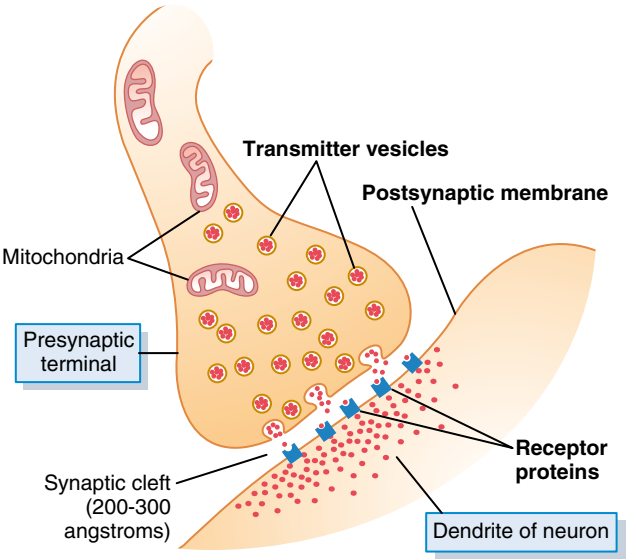


Figure 45-6 Physiologic anatomy of the synapse.

transmitter in turn causes an immediate change in permeability characteristics of the postsynaptic neuronal membrane, and this leads to excitation or inhibition of the postsynaptic neuron, depending on the neuronal receptor characteristics.

Mechanism by Which an Action Potential Causes Transmitter Release from the Presynaptic Terminals—Role of Calcium Ions

The membrane of the presynaptic terminal is called the *presynaptic membrane.* It contains large numbers of *voltage-gated calcium channels.* When an action potential depolarizes the presynaptic membrane, these calcium channels open and allow large numbers of calcium ions to flow into the terminal. The quantity of transmitter substance that is then released from the terminal into the synaptic cleft is directly related to the number of calcium ions that enter. The precise mechanism by which the calcium ions cause this release is not known, but it is believed to be the following.

When the calcium ions enter the presynaptic terminal, it is believed that they bind with special protein molecules on the inside surface of the presynaptic membrane, called *release sites.* This binding in turn causes the release sites to open through the membrane, allowing a few transmitter vesicles to release their transmitter into the cleft after each single action potential. For those vesicles that store the neurotransmitter acetylcholine, between 2000 and 10,000 molecules of acetylcholine are present in each vesicle, and there are enough vesicles in the presynaptic terminal to transmit from a few hundred to more than 10,000 action potentials.

Action of the Transmitter Substance on the Postsynaptic Neuron—Function of "Receptor Proteins"

The membrane of the postsynaptic neuron contains large numbers of *receptor proteins,* also shown in Figure 45-6. The molecules of these receptors have two important components: (1) a *binding component* that protrudes outward from the membrane into the synaptic cleft—here it binds the neurotransmitter coming from the presynaptic terminal—and (2) an *ionophore component* that passes all the way through the postsynaptic membrane to the interior of the postsynaptic neuron. The ionophore in turn is one of two types: (1) an *ion channel* that allows passage of specified types of ions through the membrane or (2) a *"second messenger" activator* that is not an ion channel but instead is a molecule that protrudes into the cell cytoplasm and activates one or more substances inside the postsynaptic neuron. These substances in turn serve as "second messengers" to increase or decrease specific cellular functions.

Ion Channels. The ion channels in the postsynaptic neuronal membrane are usually of two types: (1) *cation channels* that most often allow sodium ions to pass when opened, but sometimes allow potassium and/or calcium ions as well, and (2) *anion channels* that allow mainly chloride ions to pass but also minute quantities of other anions.

The *cation channels* that conduct sodium ions are lined with negative charges. These charges attract the positively charged sodium ions into the channel when the channel diameter increases to a size larger than that of the hydrated sodium ion. But those same negative charges *repel chloride ions and other anions* and prevent their passage.

For the *anion channels,* when the channel diameters become large enough, chloride ions pass into the channels and on through to the opposite side, whereas sodium, potassium, and calcium cations are blocked, mainly because their hydrated ions are too large to pass.

We will learn later that when cation channels open and allow positively charged sodium ions to enter, the positive electrical charges of the sodium ions will in turn excite this neuron. Therefore, a transmitter substance that opens cation channels is called an *excitatory transmitter.* Conversely, opening anion channels allows negative electrical charges to enter, which inhibits the neuron. Therefore, transmitter substances that open these channels are called *inhibitory transmitters.*

When a transmitter substance activates an ion channel, the channel usually opens within a fraction of a millisecond; when the transmitter substance is no longer present, the channel closes equally rapidly. The opening and closing of ion channels provide a means for very rapid control of postsynaptic neurons.

"Second Messenger" System in the Postsynaptic Neuron. Many functions of the nervous system—for instance, the process of memory—require prolonged changes in neurons for seconds to months after the initial transmitter substance is gone. The ion channels are not suitable for causing prolonged postsynaptic neuronal changes because these channels close within milliseconds after the transmitter substance is no longer present. However, in many instances, prolonged postsynaptic neuronal excitation or inhibition is achieved by activating a "second messenger" chemical system inside the postsynaptic neuronal cell itself, and then it is the second messenger that causes the prolonged effect.

There are several types of second messenger systems. One of the most common types uses a group of proteins called *G-proteins.* Figure 45-7 shows in the upper left corner a membrane receptor protein. A G-protein is attached to the portion of the receptor that protrudes into the interior of the cell. The G-protein in turn consists of three components: an alpha (α) component that is the *activator* portion of the G-protein and beta (β) and gamma (γ) components that are attached to the alpha component and also to the inside of the cell membrane adjacent to the receptor protein. On activation by a nerve impulse, the alpha portion of the G-protein separates from the beta and gamma portions and then is free to move within the cytoplasm of the cell.

Inside the cytoplasm, the separated alpha component performs one or more of multiple functions, depending on

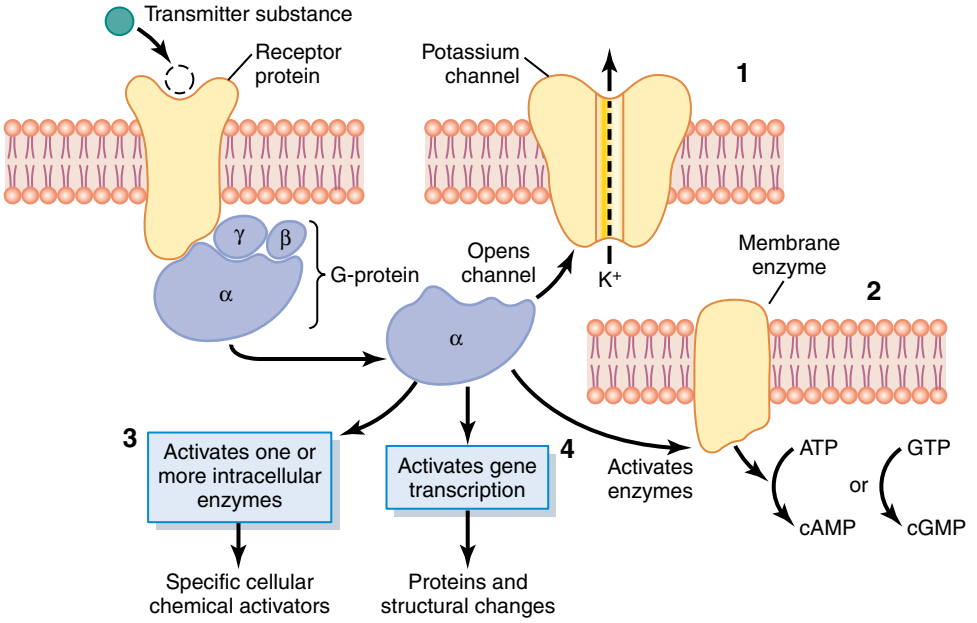


Figure 45-7 "Second messenger" system by which a transmitter substance from an initial neuron can activate a second neuron by first releasing a "G-protein" into the second neuron's cytoplasm. Four subsequent possible effects of the G-protein are shown, including *1,* opening an ion channel in the membrane of the second neuron; *2,* activating an enzyme system in the neuron's membrane; *3,* activating an intracellular enzyme system; and/or *4,* causing gene transcription in the second neuron.

the specific characteristic of each type of neuron. Shown in Figure 45-7 are four changes that can occur. They are as follows:

1. *Opening specific ion channels through the postsynaptic cell membrane.* Shown in the upper right of the figure is a potassium channel that is opened in response to the G-protein; this channel often stays open for a prolonged time, in contrast to rapid closure of directly activated ion channels that do not use the second messenger system.
2. *Activation of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP) in the neuronal cell.* Recall that either cyclic AMP or cyclic GMP can activate highly specific metabolic machinery in the neuron and, therefore, can initiate any one of many chemical results, including long-term changes in cell structure itself, which in turn alters long-term excitability of the neuron.
3. *Activation of one or more intracellular enzymes.* The G-protein can directly activate one or more intracellular enzymes. In turn the enzymes can cause any one of many specific chemical functions in the cell.
4. *Activation of gene transcription.* This is one of the most important effects of activation of the second messenger systems because gene transcription can cause formation of new proteins within the neuron, thereby changing its metabolic machinery or its structure. Indeed, it is well known that structural changes of appropriately activated neurons do occur, especially in long-term memory processes.

It is clear that activation of second messenger systems within the neuron, whether they be of the G-protein type or of other types, is extremely important for changing the long-term response characteristics of different neuronal pathways. We will return to this subject in more detail in Chapter 57 when we discuss memory functions of the nervous system.

Excitatory or Inhibitory Receptors in the Postsynaptic Membrane

Some postsynaptic receptors, when activated, cause excitation of the postsynaptic neuron, and others cause inhibition. The importance of having inhibitory, as well as excitatory, types of receptors is that this gives an additional dimension to nervous function, allowing restraint of nervous action and excitation.

The different molecular and membrane mechanisms used by the different receptors to cause excitation or inhibition include the following.

Excitation

1. Opening of sodium channels to allow large numbers of positive electrical charges to flow to the interior of the postsynaptic cell. This raises the intracellular membrane potential in the positive direction up toward the threshold level for excitation. It is by far the most widely used means for causing excitation.
2. Depressed conduction through chloride or potassium channels, or both. This decreases the diffusion of negatively charged chloride ions to the inside of the postsynaptic neuron or decreases the diffusion of positively charged potassium ions to the outside. In either instance, the effect is to make the internal membrane potential more positive than normal, which is excitatory.

3. Various changes in the internal metabolism of the postsynaptic neuron to excite cell activity or, in some instances, to increase the number of excitatory membrane receptors or decrease the number of inhibitory membrane receptors.

Inhibition

1. *Opening of chloride ion channels through the postsynaptic neuronal membrane.* This allows rapid diffusion of negatively charged chloride ions from outside the postsynaptic neuron to the inside, thereby carrying negative charges inward and increasing the negativity inside, which is inhibitory.
2. *Increase in conductance of potassium ions out of the neuron.* This allows positive ions to diffuse to the exterior, which causes increased negativity inside the neuron; this is inhibitory.
3. *Activation of receptor enzymes* that inhibit cellular metabolic functions that increase the number of inhibitory synaptic receptors or decrease the number of excitatory receptors.

Chemical Substances That Function as Synaptic Transmitters

More than 50 chemical substances have been proved or postulated to function as synaptic transmitters. Many of them are listed in Tables 45-1 and 45-2, which give two groups of synaptic transmitters. One group comprises *small-molecule, rapidly acting transmitters.* The other is made up of a large number of *neuropeptides* of much larger molecular size that are usually much more slowly acting.

Table 45-1 Small-Molecule, Rapidly Acting Transmitters

Class I
Acetylcholine
Class II: The Amines
Norepinephrine
Epinephrine
Dopamine
Serotonin
Histamine
Class III: Amino Acids
Gamma-aminobutyric acid (GABA)
Glycine
Glutamate
Aspartate
Class IV
Nitric oxide (NO)

Table 45-2 Neuropeptide, Slowly Acting Transmitters or Growth Factors

Hypothalamic-releasing hormones
Thyrotropin-releasing hormone
Luteinizing hormone–releasing hormone
Somatostatin (growth hormone inhibitory factor)
Pituitary peptides
Adrenocorticotropic hormone (ACTH)
β-Endorphin
α-Melanocyte-stimulating hormone
Prolactin
Luteinizing hormone
Thyrotropin
Growth hormone
Vasopressin
Oxytocin
Peptides that act on gut and brain
Leucine enkephalin
Methionine enkephalin
Substance P
Gastrin
Cholecystokinin
Vasoactive intestinal polypeptide (VIP)
Nerve growth factor
Brain-derived neurotropic factor
Neurotensin
Insulin
Glucagon
From other tissues
Angiotensin II
Bradykinin
Carnosine
Sleep peptides
Calcitonin

The small-molecule, rapidly acting transmitters are the ones that cause most acute responses of the nervous system, such as transmission of sensory signals to the brain and of motor signals back to the muscles. The neuropeptides, in contrast, usually cause more prolonged actions, such as long-term changes in numbers of neuronal receptors, long-term opening or closure of certain ion channels, and possibly even long-term changes in numbers of synapses or sizes of synapses.

Small-Molecule, Rapidly Acting Transmitters

In most cases, the small-molecule types of transmitters are synthesized in the cytosol of the presynaptic

terminal and are absorbed by means of active transport into the many transmitter vesicles in the terminal. Then, each time an action potential reaches the presynaptic terminal, a few vesicles at a time release their transmitter into the synaptic cleft. This usually occurs within a millisecond or less by the mechanism described earlier. The subsequent action of the small-molecule type of transmitter on the membrane receptors of the postsynaptic neuron usually also occurs within another millisecond or less. Most often the effect is to increase or decrease conductance through ion channels; an example is to increase sodium conductance, which causes excitation, or to increase potassium or chloride conductance, which causes inhibition.

Recycling of the Small-Molecule Types of Vesicles. Vesicles that store and release small-molecule transmitters are continually recycled and used over and over again. After they fuse with the synaptic membrane and open to release their transmitter substance, the vesicle membrane at first simply becomes part of the synaptic membrane. However, within seconds to minutes, the vesicle portion of the membrane invaginates back to the inside of the presynaptic terminal and pinches off to form a new vesicle. And the new vesicular membrane still contains appropriate enzyme proteins or transport proteins required for synthesizing and/or concentrating new transmitter substance inside the vesicle.

Acetylcholine is a typical small-molecule transmitter that obeys the principles of synthesis and release stated earlier. This transmitter substance is synthesized in the presynaptic terminal from acetyl coenzyme A and choline in the presence of the enzyme *choline acetyltransferase*. Then it is transported into its specific vesicles. When the vesicles later release the acetylcholine into the synaptic cleft during synaptic neuronal signal transmission, the acetylcholine is rapidly split again to acetate and choline by the enzyme *cholinesterase,* which is present in the proteoglycan reticulum that fills the space of the synaptic cleft. And then again, inside the presynaptic terminal, the vesicles are recycled; choline is actively transported back into the terminal to be used again for synthesis of new acetylcholine.

Characteristics of Some of the More Important Small-Molecule Transmitters. The most important of the small-molecule transmitters are the following.

Acetylcholine is secreted by neurons in many areas of the nervous system but specifically by (1) the terminals of the large pyramidal cells from the motor cortex, (2) several different types of neurons in the basal ganglia, (3) the motor neurons that innervate the skeletal muscles, (4) the preganglionic neurons of the autonomic nervous system, (5) the postganglionic neurons of the parasympathetic nervous system, and (6) some of the postganglionic neurons of the sympathetic nervous system. In most instances, acetylcholine has an excitatory effect; however, it is known to have inhibitory effects at some peripheral parasympathetic nerve endings, such as inhibition of the heart by the vagus nerves.

Norepinephrine is secreted by the terminals of many neurons whose cell bodies are located in the brain stem and hypothalamus. Specifically, norepinephrine-secreting neurons located in the *locus ceruleus* in the pons send nerve fibers to widespread areas of the brain to help control overall activity and mood of the mind, such as increasing the level of wakefulness. In most of these areas, norepinephrine probably activates excitatory receptors, but in a few areas, it activates inhibitory receptors instead. Norepinephrine is also secreted by most postganglionic neurons of the sympathetic nervous system, where it excites some organs but inhibits others.

Dopamine is secreted by neurons that originate in the substantia nigra. The termination of these neurons is mainly in the striatal region of the basal ganglia. The effect of dopamine is usually inhibition.

Glycine is secreted mainly at synapses in the spinal cord. It is believed to always act as an inhibitory transmitter.

GABA (gamma-aminobutyric acid) is secreted by nerve terminals in the spinal cord, cerebellum, basal ganglia, and many areas of the cortex. It is believed always to cause inhibition.

Glutamate is secreted by the presynaptic terminals in many of the sensory pathways entering the central nervous system, as well as in many areas of the cerebral cortex. It probably always causes excitation.

Serotonin is secreted by nuclei that originate in the median raphe of the brain stem and project to many brain and spinal cord areas, especially to the dorsal horns of the spinal cord and to the hypothalamus. Serotonin acts as an inhibitor of pain pathways in the cord, and an inhibitor action in the higher regions of the nervous system is believed to help control the mood of the person, perhaps even to cause sleep.

Nitric oxide is especially secreted by nerve terminals in areas of the brain responsible for long-term behavior and for memory. Therefore, this transmitter system might in the future explain some behavior and memory functions that thus far have defied understanding. Nitric oxide is different from other small-molecule transmitters in its mechanism of formation in the presynaptic terminal and in its actions on the postsynaptic neuron. It is not preformed and stored in vesicles in the presynaptic terminal as are other transmitters. Instead, it is synthesized almost instantly as needed, and it then diffuses out of the presynaptic terminals over a period of seconds rather than being released in vesicular packets. Next, it diffuses into postsynaptic neurons nearby. In the postsynaptic neuron, it usually does not greatly alter the membrane potential but instead changes intracellular metabolic functions that modify neuronal excitability for seconds, minutes, or perhaps even longer.

Neuropeptides

Neuropeptides are synthesized differently and have actions that are usually slow and in other ways quite different from those of the small-molecule transmitters. The neuropeptides are not synthesized in the cytosol of the

presynaptic terminals. Instead, they are synthesized as integral parts of large-protein molecules by ribosomes in the neuronal cell body.

The protein molecules then enter the spaces inside the endoplasmic reticulum of the cell body and subsequently inside the Golgi apparatus, where two changes occur: First, the neuropeptide-forming protein is enzymatically split into smaller fragments, some of which are either the neuropeptide itself or a precursor of it. Second, the Golgi apparatus packages the neuropeptide into minute transmitter vesicles that are released into the cytoplasm. Then the transmitter vesicles are transported all the way to the tips of the nerve fibers by *axonal streaming* of the axon cytoplasm, traveling at the slow rate of only a few centimeters per day. Finally, these vesicles release their transmitter at the neuronal terminals in response to action potentials in the same manner as for small-molecule transmitters. However, the vesicle is autolyzed and is not reused.

Because of this laborious method of forming the neuropeptides, much smaller quantities of them are usually released than of the small-molecule transmitters. This is partly compensated for by the fact that the neuropeptides are generally a thousand or more times as potent as the small-molecule transmitters. Another important characteristic of the neuropeptides is that they often cause much more prolonged actions. Some of these actions include prolonged closure of calcium channels, prolonged changes in the metabolic machinery of cells, prolonged changes in activation or deactivation of specific genes in the cell nucleus, and/or prolonged alterations in numbers of excitatory or inhibitory receptors. Some of these effects last for days, but others perhaps for months or years. Our knowledge of the functions of the neuropeptides is only beginning to develop.

Electrical Events During Neuronal Excitation

The electrical events in neuronal excitation have been studied especially in the large motor neurons of the anterior horns of the spinal cord. Therefore, the events described in the next few sections pertain essentially to these neurons. Except for quantitative differences, they apply to most other neurons of the nervous system as well.

Resting Membrane Potential of the Neuronal Soma. Figure 45-8 shows the soma of a spinal motor neuron, indicating a *resting membrane potential* of about –65 millivolts. This is somewhat less negative than the –90 millivolts found in large peripheral nerve fibers and in skeletal muscle fibers; the lower voltage is important because it allows both positive and negative control of the degree of excitability of the neuron. That is, decreasing the voltage to a less negative value makes the membrane of the neuron more excitable, whereas increasing this voltage to a more negative value makes the neuron less excitable. This is the basis for the two modes of function of the neuron—either excitation or inhibition—as explained in detail in the next sections.

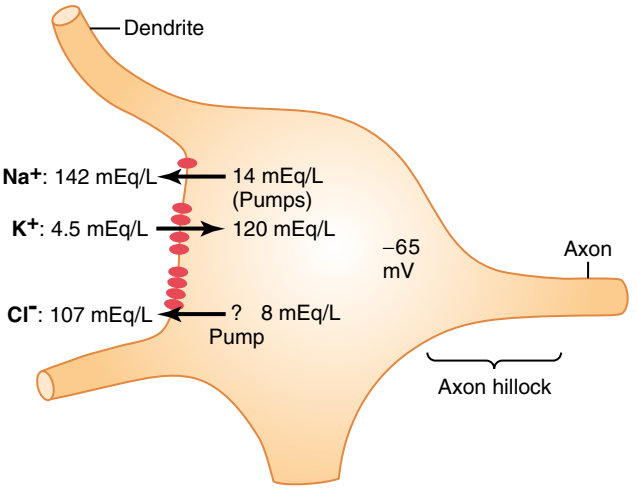


Figure 45-8 Distribution of sodium, potassium, and chloride ions across the neuronal somal membrane; origin of the intrasomal membrane potential.

Concentration Differences of Ions Across the Neuronal Somal Membrane. Figure 45-8 also shows the concentration differences across the neuronal somal membrane of the three ions that are most important for neuronal function: sodium ions, potassium ions, and chloride ions. At the top, the *sodium ion concentration* is shown to be *high in the extracellular fluid* (142 mEq/L) but *low inside the neuron* (14 mEq/L). This sodium concentration gradient is caused by a strong somal membrane sodium pump that continually pumps sodium out of the neuron.

The figure also shows that *potassium ion concentration is high inside the neuronal soma* (120 mEq/L) but *low in the extracellular fluid* (4.5 mEq/L). It shows that there is a potassium pump (the other half of the $Na^+ - K^+$ pump) that pumps potassium to the interior.

Figure 45-8 shows the *chloride ion* to be of *high concentration in the extracellular fluid* but *low concentration inside the neuron.* The membrane may be somewhat permeable to chloride ions and there may be a weak chloride pump. Yet most of the reason for the low concentration of chloride ions inside the neuron is the –65 millivolts in the neuron. That is, this negative voltage repels the negatively charged chloride ions, forcing them outward through the pores until the concentration is much less inside the membrane than outside.

Let us recall from Chapters 4 and 5 that an electrical potential across the cell membrane can oppose movement of ions through a membrane if the potential is of proper polarity and magnitude. A potential that *exactly* opposes movement of an ion is called the *Nernst potential* for that ion; the equation for this is the following:

$$\text{EMF (mV)} = \pm 61 \times \log \left(\frac{\text{Concentration inside}}{\text{Concentration outside}} \right)$$

where EMF is the Nernst potential in millivolts on the *inside of the membrane.* The potential will be negative (–) for positive ions and positive (+) for negative ions.

Now, let us calculate the Nernst potential that will exactly oppose the movement of each of the three separate ions: sodium, potassium, and chloride.

For the sodium concentration difference shown in Figure 45-8, 142 mEq/L on the exterior and 14 mEq/L on the interior, the membrane potential that will exactly oppose sodium ion movement through the sodium channels calculates to be +61 millivolts. However, the actual membrane potential is −65 millivolts, not +61 millivolts. Therefore, those sodium ions that leak to the interior are immediately pumped back to the exterior by the sodium pump, thus maintaining the −65 millivolt negative potential inside the neuron.

For potassium ions, the concentration gradient is 120 mEq/L inside the neuron and 4.5 mEq/L outside. This calculates to be a Nernst potential of −86 millivolts inside the neuron, which is more negative than the −65 that actually exists. Therefore, because of the high intracellular potassium ion concentration, there is a net tendency for potassium ions to diffuse to the outside of the neuron, but this is opposed by continual pumping of these potassium ions back to the interior.

Finally, the chloride ion gradient, 107 mEq/L outside and 8 mEq/L inside, yields a Nernst potential of −70 millivolts inside the neuron, which is only *slightly* more negative than the actual measured value of −65 millivolts. Therefore, chloride ions tend to leak very slightly to the interior of the neuron, but those few that do leak are moved back to the exterior, perhaps by an active chloride pump.

Keep these three Nernst potentials in mind and remember the direction in which the different ions tend to diffuse because this information is important in understanding both excitation and inhibition of the neuron by synapse activation or inactivation of ion channels.

Uniform Distribution of Electrical Potential Inside the Soma. The interior of the neuronal soma contains a highly conductive electrolytic solution, the *intracellular fluid* of the neuron. Furthermore, the diameter of the neuronal soma is large (from 10 to 80 micrometers), causing almost no resistance to conduction of electric current from one part of the somal interior to another part. Therefore, any change in potential in any part of the intrasomal fluid causes an almost exactly equal change in potential at all other points inside the soma (i.e., as long as the neuron is not transmitting an action potential). This is an important principle because it plays a major role in "summation" of signals entering the neuron from multiple sources, as we shall see in subsequent sections of this chapter.

Effect of Synaptic Excitation on the Postsynaptic Membrane—Excitatory Postsynaptic Potential. Figure 45-9*A* shows the resting neuron with an unexcited presynaptic terminal resting on its surface. The resting membrane potential everywhere in the soma is −65 millivolts.

Figure 45-9*B* shows a presynaptic terminal that has secreted an excitatory transmitter into the cleft between the terminal and the neuronal somal membrane. This

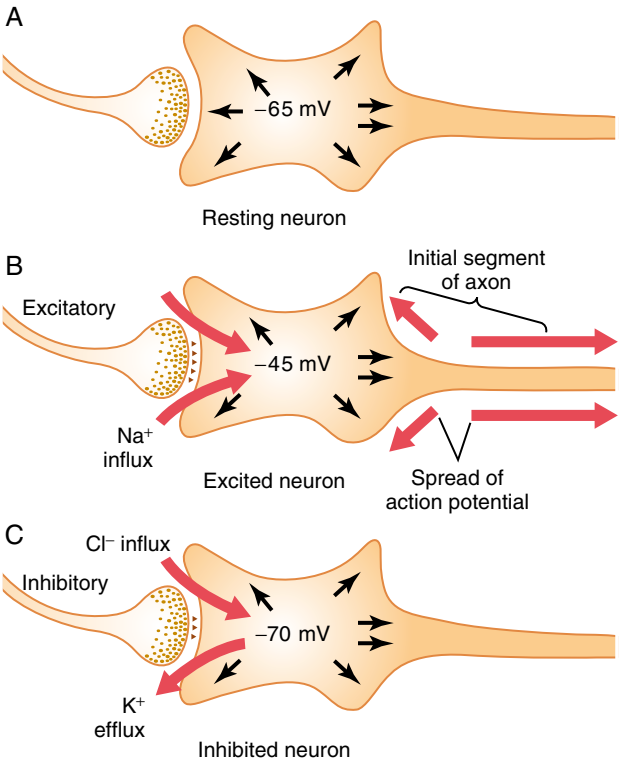


Figure 45-9 Three states of a neuron. *A*, *Resting neuron,* with a normal intraneuronal potential of −65 millivolts. *B*, Neuron in an *excited state,* with a less negative intraneuronal potential (−45 millivolts) caused by sodium influx. *C*, Neuron in an *inhibited state,* with a more negative intraneuronal membrane potential (−70 millivolts) caused by potassium ion efflux, chloride ion influx, or both.

transmitter acts on the membrane excitatory receptor *to increase the membrane's permeability to* Na^+. Because of the large sodium concentration gradient and large electrical negativity inside the neuron, sodium ions diffuse rapidly to the inside of the membrane.

The rapid influx of positively charged sodium ions to the interior neutralizes part of the negativity of the resting membrane potential. Thus, in Figure 45-9*B,* the resting membrane potential has increased in the positive direction from −65 to −45 millivolts. This positive increase in voltage above the normal resting neuronal potential—that is, to a less negative value—is called the *excitatory postsynaptic potential* (or EPSP) because if this potential rises high enough in the positive direction, it will elicit an action potential in the postsynaptic neuron, thus exciting it. (In this case, the EPSP is +20 millivolts—i.e., 20 millivolts more positive than the resting value.)

However, we must issue a word of warning. Discharge of a single presynaptic terminal can never increase the neuronal potential from −65 millivolts all the way up to −45 millivolts. An increase of this magnitude requires simultaneous discharge of many terminals—about 40 to 80 for the usual anterior motor neuron—at the same time or in rapid succession. This occurs by a process called *summation,* which is discussed in detail in the next sections.

Generation of Action Potentials in the Initial Segment of the Axon Leaving the Neuron—Threshold for Excitation. When the EPSP rises high enough in the positive direction, there comes a point at which this initiates an action potential in the neuron. However, the action potential does not begin adjacent to the excitatory synapses. Instead, *it begins in the initial segment of the axon* where the axon leaves the neuronal soma. The main reason for this point of origin of the action potential is that the soma has relatively few voltage-gated sodium channels in its membrane, which makes it difficult for the EPSP to open the required number of sodium channels to elicit an action potential. Conversely, *the membrane of the initial segment* has seven times as great a concentration of voltage-gated sodium channels as does the soma and, therefore, can generate an action potential with much greater ease than can the soma. The EPSP that will elicit an action potential in the axon initial segment is between +10 and +20 millivolts. This is in contrast to the +30 or +40 millivolts or more required on the soma.

Once the action potential begins, it travels peripherally along the axon and usually also backward over the soma. In some instances it travels backward into the dendrites but not into all of them because they, like the neuronal soma, have very few voltage-gated sodium channels and therefore frequently cannot generate action potentials at all. Thus, in Figure 45-9*B,* the *threshold* for excitation of the neuron is shown to be about –45 millivolts, which represents an EPSP of +20 millivolts—that is, 20 millivolts more positive than the normal resting neuronal potential of –65 millivolts.

Electrical Events During Neuronal Inhibition

Effect of Inhibitory Synapses on the Postsynaptic Membrane—Inhibitory Postsynaptic Potential. The inhibitory synapses *open mainly chloride channels,* allowing easy passage of chloride ions. Now, to understand how the inhibitory synapses inhibit the postsynaptic neuron, we must recall what we learned about the Nernst potential for chloride ions. We calculated the Nernst potential for chloride ions to be about –70 millivolts. This potential is more negative than the –65 millivolts normally present inside the resting neuronal membrane. Therefore, opening the chloride channels will allow negatively charged chloride ions to move from the extracellular fluid to the interior, which will make the interior membrane potential more negative than normal, approaching the –70 millivolt level.

Opening potassium channels will allow positively charged potassium ions to move to the exterior, and this will also make the interior membrane potential more negative than usual. Thus, both chloride influx and potassium efflux increase the degree of intracellular negativity, which is called *hyperpolarization.* This inhibits the neuron because the membrane potential is even more negative than the normal intracellular potential. Therefore, an increase in negativity beyond the normal resting membrane potential level is called an *inhibitory postsynaptic potential* (IPSP).

Figure 45-9*C* shows the effect on the membrane potential caused by activation of inhibitory synapses, allowing chloride influx into the cell and/or potassium efflux out of the cell, with the membrane potential decreasing from its normal value of –65 millivolts to the more negative value of –70 millivolts. This membrane potential is 5 millivolts more negative than normal and is therefore an IPSP of –5 millivolts, which inhibits transmission of the nerve signal through the synapse.

Presynaptic Inhibition

In addition to inhibition caused by inhibitory synapses operating at the neuronal membrane, which is called *postsynaptic inhibition,* another type of inhibition often occurs at the presynaptic terminals before the signal ever reaches the synapse. This type of inhibition, called *presynaptic inhibition,* occurs in the following way.

Presynaptic inhibition is caused by release of an inhibitory substance onto the outsides of the presynaptic nerve fibrils before their own endings terminate on the postsynaptic neuron. *In most instances, the inhibitory transmitter substance is GABA (gamma-aminobutyric acid).* This has a specific effect of opening anion channels, allowing large numbers of chloride ions to diffuse into the terminal fibril. The negative charges of these ions inhibit synaptic transmission because they cancel much of the excitatory effect of the positively charged sodium ions that also enter the terminal fibrils when an action potential arrives.

Presynaptic inhibition occurs in many of the sensory pathways in the nervous system. In fact, adjacent sensory nerve fibers often mutually inhibit one another, which minimizes sideways spread and mixing of signals in sensory tracts. We discuss the importance of this phenomenon more fully in subsequent chapters.

Time Course of Postsynaptic Potentials

When an excitatory synapse excites the anterior motor neuron, the neuronal membrane becomes highly permeable to sodium ions for 1 to 2 milliseconds. During this very short time, enough sodium ions diffuse rapidly to the interior of the postsynaptic motor neuron to increase its intraneuronal potential by a few millivolts, thus creating the excitatory postsynaptic potential (EPSP) shown by the blue and green curves of Figure 45-10. This potential then slowly declines over the next 15 milliseconds because this is the time required for the excess positive charges to leak out of the excited neuron and to re-establish the normal resting membrane potential.

Precisely the opposite effect occurs for an IPSP; that is, the inhibitory synapse increases the permeability of the membrane to potassium or chloride ions, or both, for 1 to 2 milliseconds, and this decreases the intraneuronal potential to a more negative value than normal, thereby creating the IPSP. This potential also dies away in about 15 milliseconds.

Other types of transmitter substances can excite or inhibit the postsynaptic neuron for much longer

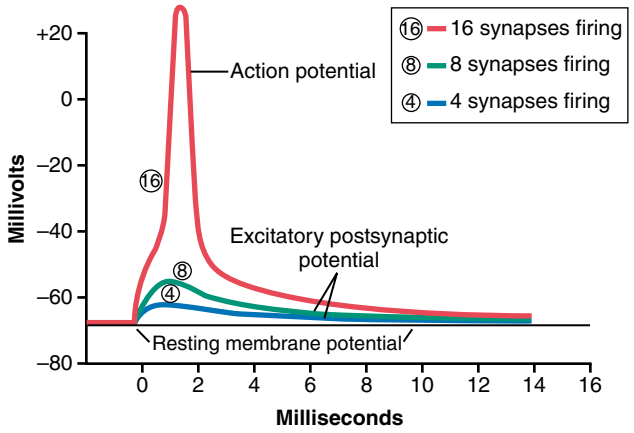


Figure 45-10 Excitatory postsynaptic potentials, showing that simultaneous firing of only a few synapses will not cause sufficient summated potential to elicit an action potential, but that simultaneous firing of many synapses will raise the summated potential to threshold for excitation and cause a superimposed action potential.

periods—for hundreds of milliseconds or even for seconds, minutes, or hours. This is especially true for some of the neuropeptide transmitters.

"Spatial Summation" in Neurons—Threshold for Firing

Excitation of a single presynaptic terminal on the surface of a neuron almost never excites the neuron. The reason for this is that the amount of transmitter substance released by a single terminal to cause an EPSP is usually no greater than 0.5 to 1 millivolt, instead of the 10 to 20 millivolts normally required to reach threshold for excitation.

However, many presynaptic terminals are usually stimulated at the same time. Even though these terminals are spread over wide areas of the neuron, their effects can still *summate;* that is, they can add to one another until neuronal excitation does occur. The reason for this is the following: It was pointed out earlier that a change in potential at any single point within the soma will cause the potential to change everywhere inside the soma almost equally. This is true because of the very high electrical conductivity inside the large neuronal cell body. Therefore, for each excitatory synapse that discharges simultaneously, the total intrasomal potential becomes more positive by 0.5 to 1.0 millivolt. When the EPSP becomes great enough, the *threshold for firing* will be reached and an action potential will develop spontaneously in the initial segment of the axon. This is demonstrated in Figure 45-10. The bottom postsynaptic potential in the figure was caused by simultaneous stimulation of 4 synapses; the next higher potential was caused by stimulation of 8 synapses; finally, a still higher EPSP was caused by stimulation of 16 synapses. In this last instance, the firing threshold had been reached, and an action potential was generated in the axon.

This effect of summing simultaneous postsynaptic potentials by activating multiple terminals on widely spaced areas of the neuronal membrane is called *spatial summation.*

"Temporal Summation" Caused by Successive Discharges of a Presynaptic Terminal

Each time a presynaptic terminal fires, the released transmitter substance opens the membrane channels for at most a millisecond or so. But the changed postsynaptic potential lasts up to 15 milliseconds after the synaptic membrane channels have already closed. Therefore, a second opening of the same channels can increase the postsynaptic potential to a still greater level, and the more rapid the rate of stimulation, the greater the postsynaptic potential becomes. Thus, successive discharges from a single presynaptic terminal, if they occur rapidly enough, can add to one another; that is, they can "summate." This type of summation is called *temporal summation.*

Simultaneous Summation of Inhibitory and Excitatory Postsynaptic Potentials. If an IPSP is tending to *decrease* the membrane potential to a more negative value while an EPSP is tending to *increase* the potential at the same time, these two effects can either completely or partially nullify each other. Thus, if a neuron is being excited by an EPSP, an inhibitory signal from another source can often reduce the postsynaptic potential to less than threshold value for excitation, thus turning off the activity of the neuron.

"Facilitation" of Neurons

Often the summated postsynaptic potential is excitatory but has not risen high enough to reach the threshold for firing by the postsynaptic neuron. When this happens, the neuron is said to be *facilitated.* That is, its membrane potential is nearer the threshold for firing than normal, but not yet at the firing level. Consequently, another excitatory signal entering the neuron from some other source can then excite the neuron very easily. Diffuse signals in the nervous system often do facilitate large groups of neurons so that they can respond quickly and easily to signals arriving from other sources.

Special Functions of Dendrites for Exciting Neurons

Large Spatial Field of Excitation of the Dendrites. The dendrites of the anterior motor neurons often extend 500 to 1000 micrometers in all directions from the neuronal soma. And these dendrites can receive signals from a large spatial area around the motor neuron. This provides a vast opportunity for summation of signals from many separate presynaptic nerve fibers.

It is also important that between 80 and 95 percent of all the presynaptic terminals of the anterior motor neuron terminate on dendrites, in contrast to only 5 to 20 percent terminating on the neuronal soma. Therefore, a large

share of the excitation is provided by signals transmitted by way of the dendrites.

Most Dendrites Cannot Transmit Action Potentials, but They Can Transmit Signals Within the Same Neuron by Electrotonic Conduction. Most dendrites fail to transmit action potentials because their membranes have relatively few voltage-gated sodium channels, and their thresholds for excitation are too high for action potentials to occur. Yet they do transmit *electrotonic current* down the dendrites to the soma. Transmission of electrotonic current means direct spread of electrical current by ion conduction in the fluids of the dendrites but without generation of action potentials. Stimulation (or inhibition) of the neuron by this current has special characteristics, as follows.

Decrement of Electrotonic Conduction in the Dendrites—Greater Excitatory (or Inhibitory) Effect by Synapses Located Near the Soma. In Figure 45-11, multiple excitatory and inhibitory synapses are shown stimulating the dendrites of a neuron. On the two dendrites to the left, there are excitatory effects near the tip ends; note the high levels of excitatory postsynaptic potentials at these ends—that is, note the *less negative* membrane potentials at these points. However, a large share of the excitatory postsynaptic potential is lost before it reaches the soma. The reason is that the dendrites are long, and their membranes are thin and at least partially permeable to potassium and chloride ions, making them "leaky" to electric current. Therefore, before the excitatory potentials can reach the soma, a large share of the potential is lost by leakage through the membrane. This decrease in membrane potential as it spreads

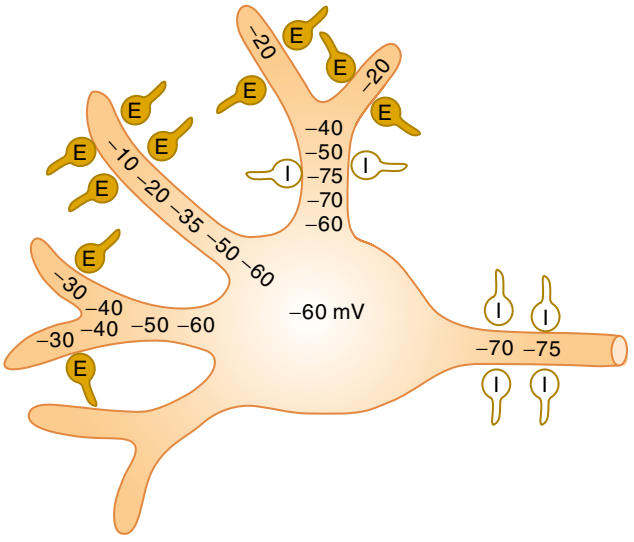


Figure 45-11 Stimulation of a neuron by presynaptic terminals located on dendrites, showing, especially, decremental conduction of excitatory (*E*) electrotonic potentials in the two dendrites to the left and inhibition (*I*) of dendritic excitation in the dendrite that is uppermost. A powerful effect of inhibitory synapses at the initial segment of the axon is also shown.

electrotonically along dendrites toward the soma is called *decremental conduction.*

The farther the excitatory synapse is from the soma of the neuron, the greater will be the decrement and the lesser will be excitatory signal reaching the soma. Therefore, those synapses that lie near the soma have far more effect in causing neuron excitation or inhibition than those that lie far away from the soma.

Summation of Excitation and Inhibition in Dendrites. The uppermost dendrite of Figure 45-11 is shown to be stimulated by both excitatory and inhibitory synapses. At the tip of the dendrite is a strong excitatory postsynaptic potential, but nearer the soma are two inhibitory synapses acting on the same dendrite. These inhibitory synapses provide a hyperpolarizing voltage that completely nullifies the excitatory effect and indeed transmits a small amount of inhibition by electrotonic conduction toward the soma. Thus, dendrites can summate excitatory and inhibitory postsynaptic potentials in the same way that the soma can. Also shown in the figure are several inhibitory synapses located directly on the axon hillock and initial axon segment. This location provides especially powerful inhibition because it has the direct effect of increasing the threshold for excitation at the very point where the action potential is normally generated.

Relation of State of Excitation of the Neuron to Rate of Firing

"Excitatory State." The "excitatory state" of a neuron is defined as the summated degree of excitatory drive to the neuron. If there is a higher degree of excitation than inhibition of the neuron at any given instant, then it is said that there is an *excitatory state.* Conversely, if there is more inhibition than excitation, then it is said that there is an *inhibitory state.*

When the excitatory state of a neuron rises above the threshold for excitation, the neuron will fire repetitively as long as the excitatory state remains at that level. Figure 45-12 shows responses of three types of neurons

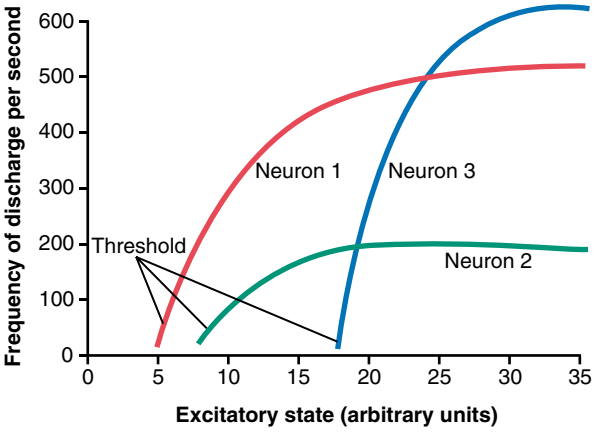


Figure 45-12 Response characteristics of different types of neurons to different levels of excitatory state.

to varying levels of excitatory state. Note that neuron 1 has a low threshold for excitation, whereas neuron 3 has a high threshold. But note also that neuron 2 has the lowest maximum frequency of discharge, whereas neuron 3 has the highest maximum frequency.

Some neurons in the central nervous system fire continuously because even the normal excitatory state is above the threshold level. Their frequency of firing can usually be increased still more by further increasing their excitatory state. The frequency can be decreased, or firing can even be stopped, by superimposing an inhibitory state on the neuron. Thus, different neurons respond differently, have different thresholds for excitation, and have widely differing maximum frequencies of discharge. With a little imagination, one can readily understand the importance of having different neurons with these many types of response characteristics to perform the widely varying functions of the nervous system.

Some Special Characteristics of Synaptic Transmission

Fatigue of Synaptic Transmission. When excitatory synapses are repetitively stimulated at a rapid rate, the number of discharges by the postsynaptic neuron is at first very great, but the firing rate becomes progressively less in succeeding milliseconds or seconds. This is called *fatigue* of synaptic transmission.

Fatigue is an exceedingly important characteristic of synaptic function because when areas of the nervous system become overexcited, fatigue causes them to lose this excess excitability after a while. For example, fatigue is probably the most important means by which the excess excitability of the brain during an epileptic seizure is finally subdued so that the seizure ceases. Thus, the development of fatigue is a protective mechanism against excess neuronal activity. This is discussed further in the description of reverberating neuronal circuits in Chapter 46.

The mechanism of fatigue is mainly exhaustion or partial exhaustion of the stores of transmitter substance in the presynaptic terminals. The excitatory terminals on many neurons can store enough excitatory transmitter to cause only about 10,000 action potentials, and the transmitter can be exhausted in only a few seconds to a few minutes of rapid stimulation. Part of the fatigue process probably results from two other factors as well: (1) progressive inactivation of many of the postsynaptic membrane receptors and (2) slow development of abnormal concentrations of ions inside the *postsynaptic* neuronal cell.

Effect of Acidosis or Alkalosis on Synaptic Transmission. Most neurons are highly responsive to changes in pH of the surrounding interstitial fluids. *Normally, alkalosis greatly increases neuronal excitability.* For instance, a rise in arterial blood pH from the 7.4 norm to 7.8 to 8.0 often causes cerebral epileptic seizures because of increased excitability of some or all of the cerebral neurons. This can be demonstrated especially well by asking a person who is predisposed to epileptic seizures to overbreathe. The overbreathing blows off carbon dioxide and therefore elevates the pH of the blood momentarily, but even this short time can often precipitate an epileptic attack.

Conversely, *acidosis greatly depresses neuronal activity;* a fall in pH from 7.4 to below 7.0 usually causes a comatose state. For instance, in very severe diabetic or uremic acidosis, coma virtually always develops.

Effect of Hypoxia on Synaptic Transmission. Neuronal excitability is also highly dependent on an adequate supply of oxygen. Cessation of oxygen for only a few seconds can cause complete inexcitability of some neurons. This is observed when the brain's blood flow is temporarily interrupted because within 3 to 7 seconds, the person becomes unconscious.

Effect of Drugs on Synaptic Transmission. Many drugs are known to increase the excitability of neurons, and others are known to decrease excitability. For instance, *caffeine, theophylline,* and *theobromine,* which are found in coffee, tea, and cocoa, respectively, all *increase* neuronal excitability, presumably by reducing the threshold for excitation of neurons.

Strychnine is one of the best known of all agents that increase excitability of neurons. However, it does not do this by reducing the threshold for excitation of the neurons; instead, it *inhibits the action of some normally inhibitory transmitter substances,* especially the inhibitory effect of glycine in the spinal cord. Therefore, the effects of the excitatory transmitters become overwhelming, and the neurons become so excited that they go into rapidly repetitive discharge, resulting in severe tonic muscle spasms.

Most anesthetics increase the neuronal membrane threshold for excitation and thereby decrease synaptic transmission at many points in the nervous system. Because many of the anesthetics are especially lipid soluble, it has been reasoned that some of them might change the physical characteristics of the neuronal membranes, making them less responsive to excitatory agents.

Synaptic Delay. During transmission of a neuronal signal from a presynaptic neuron to a postsynaptic neuron, a certain amount of time is consumed in the process of (1) discharge of the transmitter substance by the presynaptic terminal, (2) diffusion of the transmitter to the postsynaptic neuronal membrane, (3) action of the transmitter on the membrane receptor, (4) action of the receptor to increase the membrane permeability, and (5) inward diffusion of sodium to raise the excitatory postsynaptic potential to a high enough level to elicit an action potential. The *minimal* period of time required for all these events to take place, even when large numbers of excitatory synapses are stimulated simultaneously, is about 0.5 millisecond. This is called the *synaptic delay.* Neurophysiologists can measure the *minimal* delay time

between an input volley of impulses into a pool of neurons and the consequent output volley. From the measure of delay time, one can then estimate the number of series neurons in the circuit.

Bibliography

Alberini CM: Transcription factors in long-term memory and synaptic plasticity, *Physiol Rev* 89:121, 2009.

Bloodgood BL, Sabatini BL: Regulation of synaptic signalling by postsynaptic, non-glutamate receptor ion channels, *J Physiol* 586:1475, 2008.

Ben-Ari Y, Gaiarsa JL, Tyzio R, et al: GABA: a pioneer transmitter that excites immature neurons and generates primitive oscillations, *Physiol Rev* 87:1215, 2007.

Boehning D, Snyder SH: Novel neural modulators, *Annu Rev Neurosci* 26:105, 2003.

Brasnjo G, Otis TS: Glycine transporters not only take out the garbage, they recycle, *Neuron* 40:667, 2003.

Conde C, Cáceres A: Microtubule assembly, organization and dynamics in axons and dendrites, *Nat Rev Neurosci* 10:319, 2009.

Dalva MB, McClelland AC, Kayser MS: Cell adhesion molecules: signalling functions at the synapse, *Nat Rev Neurosci* 8:206, 2007.

Deeg KE: Synapse-specific homeostatic mechanisms in the hippocampus, *J Neurophysiol* 101:503, 2009.

Engelman HS, MacDermott AB: Presynaptic inotropic receptors and control of transmitter release, *Nat Rev Neurosci* 5:135, 2004.

Haines DE, Lancon JA: *Review of Neuroscience*, New York, 2003, Churchill Livingstone.

Jacob TC, Moss SJ, Jurd R: GABA(A) receptor trafficking and its role in the dynamic modulation of neuronal inhibition, *Nat Rev Neurosci* 9(5):331–343, 2008 May.

Kandel ER: The molecular biology of memory storage: a dialogue between genes and synapses, *Science* 294:1030, 2001.

Kandel ER, Schwartz JH, Jessell TM: *Principles of Neural Science*, ed 4, New York, 2000, McGraw-Hill.

Kerchner GA, Nicoll RA: Silent synapses and the emergence of a postsynaptic mechanism for LTP, *Nat Rev Neurosci* 9:813, 2008.

Klein R: Bidirectional modulation of synaptic functions by Eph/ephrin signaling, *Nat Neurosci* 12:15, 2009.

Lisman JE, Raghavachari S, Tsien RW: The sequence of events that underlie quantal transmission at central glutamatergic synapses, *Nat Rev Neurosci* 8:597, 2007.

Magee JC: Dendritic integration of excitatory synaptic input, *Nat Rev Neurosci* 1:181, 2000.

Migliore M, Shepherd GM: Emerging rules for the distributions of active dendritic conductances, *Nat Rev Neurosci* 3:362, 2002.

Muller D, Nikonenko I: Dynamic presynaptic varicosities: a role in activity-dependent synaptogenesis, *Trends Neurosci* 26:573, 2003.

Prast H, Philippu A: Nitric oxide as modulator of neuronal function, *Prog Neurobiol* 64:51, 2001.

Reid CA, Bekkers JM, Clements JD: Presynaptic Ca^{2+} channels: a functional patchwork, *Trends Neurosci* 26:683, 2003.

Robinson RB, Siegelbaum SA: Hyperpolarization-activated cation currents: from molecules to physiological function, *Annu Rev Physiol* 65:453, 2003.

Ruff RL: Neurophysiology of the neuromuscular junction: overview, *Ann N Y Acad Sci* 998:1, 2003.

Schmolesky MT, Weber JT, De Zeeuw CI, et al: The making of a complex spike: ionic composition and plasticity, *Ann N Y Acad Sci* 978:359, 2002.

Semyanov A, Walker MC, Kullmann DM, et al: Tonically active GABA A receptors: modulating gain and maintaining the tone, *Trends Neurosci* 27:262, 2004.

Sjöström PJ, Rancz EA, Roth A, et al: Dendritic excitability and synaptic plasticity, *Physiol Rev* 88:769, 2008.

Spruston N: Pyramidal neurons: dendritic structure and synaptic integration, *Nat Rev Neurosci* 9:206, 2008.

Williams SR, Wozny C, Mitchell SJ: The back and forth of dendritic plasticity, *Neuron* 56:947, 2007.

Zucker RS, Regehr WG: Short-term synaptic plasticity, *Annu Rev Physiol* 64:355, 2002.