



**Course Title: Anatomy & Physiology: Digestive, Respiratory, and Urinary Systems**

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# Anatomy & Physiology

## (chapters 22 to 26)

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# 22 | THE RESPIRATORY SYSTEM



**Figure 22.1 Mountain Climbers** The thin air at high elevations can strain the human respiratory system. (credit: "bortescristian"/flickr.com)

## Introduction

### Chapter Objectives

After studying this chapter, you will be able to:

- List the structures of the respiratory system
- List the major functions of the respiratory system
- Outline the forces that allow for air movement into and out of the lungs
- Outline the process of gas exchange
- Summarize the process of oxygen and carbon dioxide transport within the respiratory system
- Create a flow chart illustrating how respiration is controlled
- Discuss how the respiratory system responds to exercise
- Describe the development of the respiratory system in the embryo

Hold your breath. Really! See how long you can hold your breath as you continue reading...How long can you do it? Chances are you are feeling uncomfortable already. A typical human cannot survive without breathing for more than 3 minutes, and even if you wanted to hold your breath longer, your autonomic nervous system would take control. This is

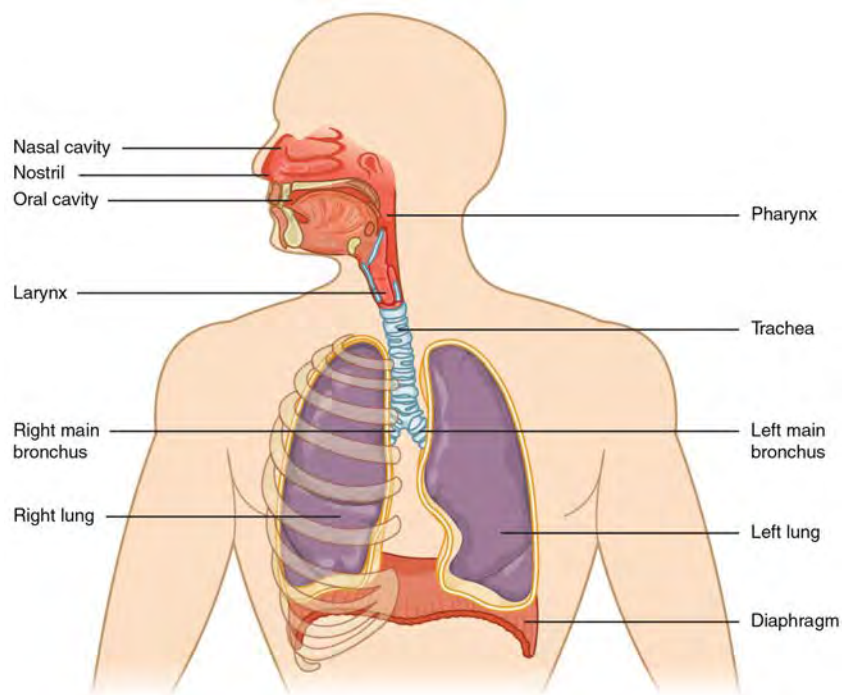
because every cell in the body needs to run the oxidative stages of cellular respiration, the process by which energy is produced in the form of adenosine triphosphate (ATP). For oxidative phosphorylation to occur, oxygen is used as a reactant and carbon dioxide is released as a waste product. You may be surprised to learn that although oxygen is a critical need for cells, it is actually the accumulation of carbon dioxide that primarily drives your need to breathe. Carbon dioxide is exhaled and oxygen is inhaled through the respiratory system, which includes muscles to move air into and out of the lungs, passageways through which air moves, and microscopic gas exchange surfaces covered by capillaries. The circulatory system transports gases from the lungs to tissues throughout the body and vice versa. A variety of diseases can affect the respiratory system, such as asthma, emphysema, chronic obstruction pulmonary disorder (COPD), and lung cancer. All of these conditions affect the gas exchange process and result in labored breathing and other difficulties.

## 22.1 | Organs and Structures of the Respiratory System

By the end of this section, you will be able to:

- List the structures that make up the respiratory system
- Describe how the respiratory system processes oxygen and CO<sub>2</sub>
- Compare and contrast the functions of upper respiratory tract with the lower respiratory tract

The major organs of the respiratory system function primarily to provide oxygen to body tissues for cellular respiration, remove the waste product carbon dioxide, and help to maintain acid-base balance. Portions of the respiratory system are also used for non-vital functions, such as sensing odors, speech production, and for straining, such as during childbirth or coughing (Figure 22.2).



**Figure 22.2 Major Respiratory Structures** The major respiratory structures span the nasal cavity to the diaphragm.

Functionally, the respiratory system can be divided into a conducting zone and a respiratory zone. The **conducting zone** of the respiratory system includes the organs and structures not directly involved in gas exchange. The gas exchange occurs in the **respiratory zone**.

### Conducting Zone

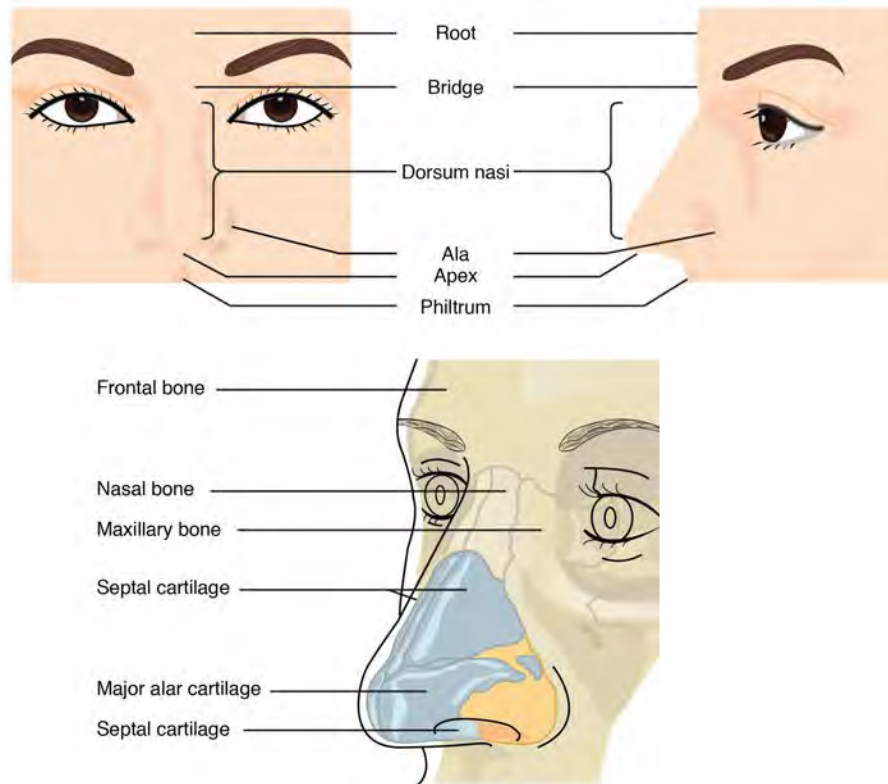
The major functions of the conducting zone are to provide a route for incoming and outgoing air, remove debris and pathogens from the incoming air, and warm and humidify the incoming air. Several structures within the conducting zone

perform other functions as well. The epithelium of the nasal passages, for example, is essential to sensing odors, and the bronchial epithelium that lines the lungs can metabolize some airborne carcinogens.

### The Nose and its Adjacent Structures

The major entrance and exit for the respiratory system is through the nose. When discussing the nose, it is helpful to divide it into two major sections: the external nose, and the nasal cavity or internal nose.

The **external nose** consists of the surface and skeletal structures that result in the outward appearance of the nose and contribute to its numerous functions (**Figure 22.3**). The **root** is the region of the nose located between the eyebrows. The **bridge** is the part of the nose that connects the root to the rest of the nose. The **dorsum nasi** is the length of the nose. The **apex** is the tip of the nose. On either side of the apex, the nostrils are formed by the alae (singular = ala). An **ala** is a cartilaginous structure that forms the lateral side of each **naris** (plural = nares), or nostril opening. The **philtrum** is the concave surface that connects the apex of the nose to the upper lip.

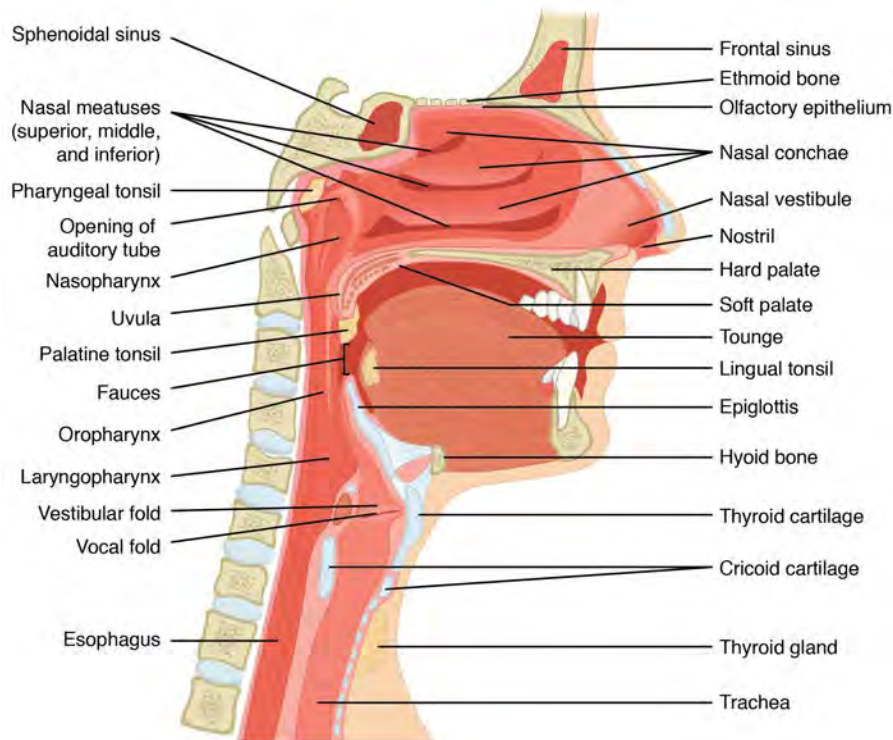


**Figure 22.3 Nose** This illustration shows features of the external nose (top) and skeletal features of the nose (bottom).

Underneath the thin skin of the nose are its skeletal features (see **Figure 22.3**, lower illustration). While the root and bridge of the nose consist of bone, the protruding portion of the nose is composed of cartilage. As a result, when looking at a skull, the nose is missing. The **nasal bone** is one of a pair of bones that lies under the root and bridge of the nose. The nasal bone articulates superiorly with the frontal bone and laterally with the maxillary bones. Septal cartilage is flexible hyaline cartilage connected to the nasal bone, forming the dorsum nasi. The **alar cartilage** consists of the apex of the nose; it surrounds the naris.

The nares open into the nasal cavity, which is separated into left and right sections by the nasal septum (**Figure 22.4**). The **nasal septum** is formed anteriorly by a portion of the septal cartilage (the flexible portion you can touch with your fingers) and posteriorly by the perpendicular plate of the ethmoid bone (a cranial bone located just posterior to the nasal bones) and the thin vomer bones (whose name refers to its plough shape). Each lateral wall of the nasal cavity has three bony projections, called the superior, middle, and inferior nasal conchae. The inferior conchae are separate bones, whereas the superior and middle conchae are portions of the ethmoid bone. Conchae serve to increase the surface area of the nasal cavity and to disrupt the flow of air as it enters the nose, causing air to bounce along the epithelium, where it is cleaned and warmed. The conchae and **meatuses** also conserve water and prevent dehydration of the nasal epithelium by trapping water

during exhalation. The floor of the nasal cavity is composed of the palate. The hard palate at the anterior region of the nasal cavity is composed of bone. The soft palate at the posterior portion of the nasal cavity consists of muscle tissue. Air exits the nasal cavities via the internal nares and moves into the pharynx.

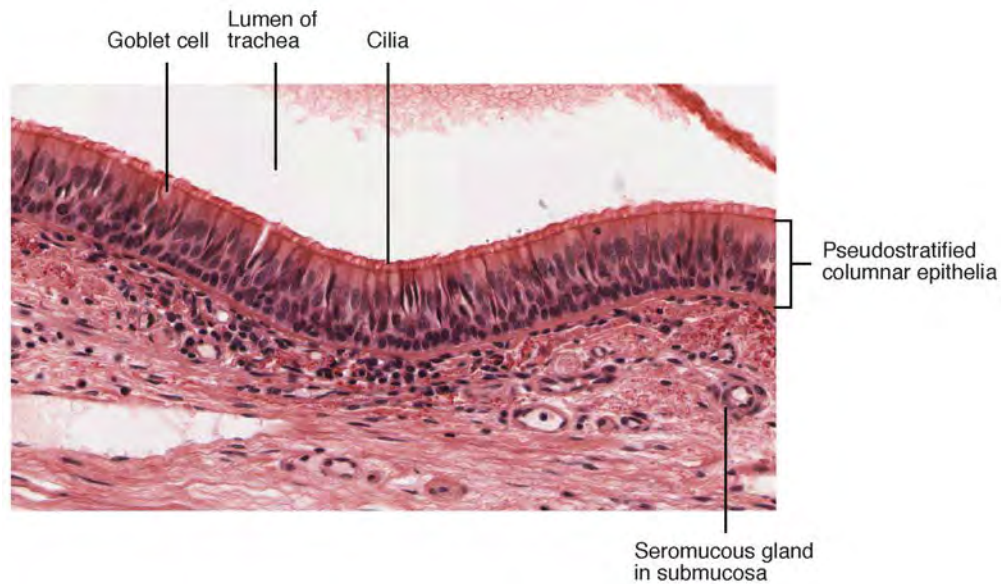


**Figure 22.4 Upper Airway**

Several bones that help form the walls of the nasal cavity have air-containing spaces called the paranasal sinuses, which serve to warm and humidify incoming air. Sinuses are lined with a mucosa. Each **paranasal sinus** is named for its associated bone: frontal sinus, maxillary sinus, sphenoidal sinus, and ethmoidal sinus. The sinuses produce mucus and lighten the weight of the skull.

The nares and anterior portion of the nasal cavities are lined with mucous membranes, containing sebaceous glands and hair follicles that serve to prevent the passage of large debris, such as dirt, through the nasal cavity. An olfactory epithelium used to detect odors is found deeper in the nasal cavity.

The conchae, meatuses, and paranasal sinuses are lined by **respiratory epithelium** composed of pseudostratified ciliated columnar epithelium (**Figure 22.5**). The epithelium contains goblet cells, one of the specialized, columnar epithelial cells that produce mucus to trap debris. The cilia of the respiratory epithelium help remove the mucus and debris from the nasal cavity with a constant beating motion, sweeping materials towards the throat to be swallowed. Interestingly, cold air slows the movement of the cilia, resulting in accumulation of mucus that may in turn lead to a runny nose during cold weather. This moist epithelium functions to warm and humidify incoming air. Capillaries located just beneath the nasal epithelium warm the air by convection. Serous and mucus-producing cells also secrete the lysozyme enzyme and proteins called defensins, which have antibacterial properties. Immune cells that patrol the connective tissue deep to the respiratory epithelium provide additional protection.



**Figure 22.5 Pseudostratified Ciliated Columnar Epithelium** Respiratory epithelium is pseudostratified ciliated columnar epithelium. Seromucous glands provide lubricating mucus. LM  $\times$  680. (Micrograph provided by the Regents of University of Michigan Medical School  $\copyright$  2012)

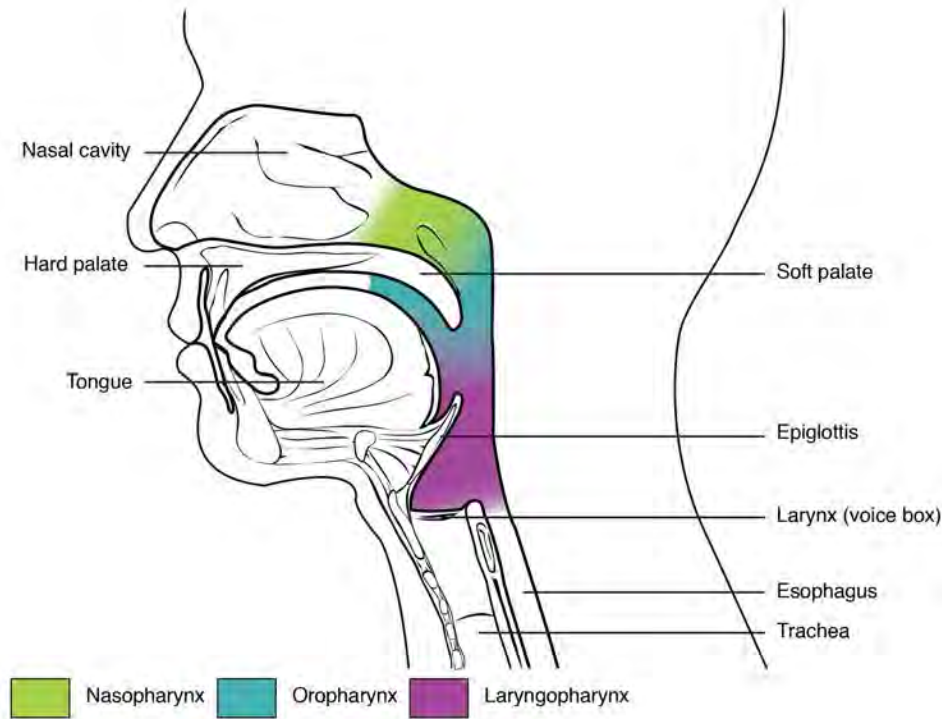
## Interactive LINK



View the University of Michigan WebScope at [http://141.214.65.171/Histology/Basic%20Tissues/Epithelium%20and%20CT/040\\_HISTO\\_40X.svs/view.apml?](http://141.214.65.171/Histology/Basic%20Tissues/Epithelium%20and%20CT/040_HISTO_40X.svs/view.apml?) (<http://openstaxcollege.org/l/pseudoMG>) to explore the tissue sample in greater detail.

## Pharynx

The **pharynx** is a tube formed by skeletal muscle and lined by mucous membrane that is continuous with that of the nasal cavities (see **Figure 22.4**). The pharynx is divided into three major regions: the nasopharynx, the oropharynx, and the laryngopharynx (**Figure 22.6**).



**Figure 22.6 Divisions of the Pharynx** The pharynx is divided into three regions: the nasopharynx, the oropharynx, and the laryngopharynx.

The **nasopharynx** is flanked by the conchae of the nasal cavity, and it serves only as an airway. At the top of the nasopharynx are the pharyngeal tonsils. A **pharyngeal tonsil**, also called an adenoid, is an aggregate of lymphoid reticular tissue similar to a lymph node that lies at the superior portion of the nasopharynx. The function of the pharyngeal tonsil is not well understood, but it contains a rich supply of lymphocytes and is covered with ciliated epithelium that traps and destroys invading pathogens that enter during inhalation. The pharyngeal tonsils are large in children, but interestingly, tend to regress with age and may even disappear. The uvula is a small bulbous, teardrop-shaped structure located at the apex of the soft palate. Both the uvula and soft palate move like a pendulum during swallowing, swinging upward to close off the nasopharynx to prevent ingested materials from entering the nasal cavity. In addition, auditory (Eustachian) tubes that connect to each middle ear cavity open into the nasopharynx. This connection is why colds often lead to ear infections.

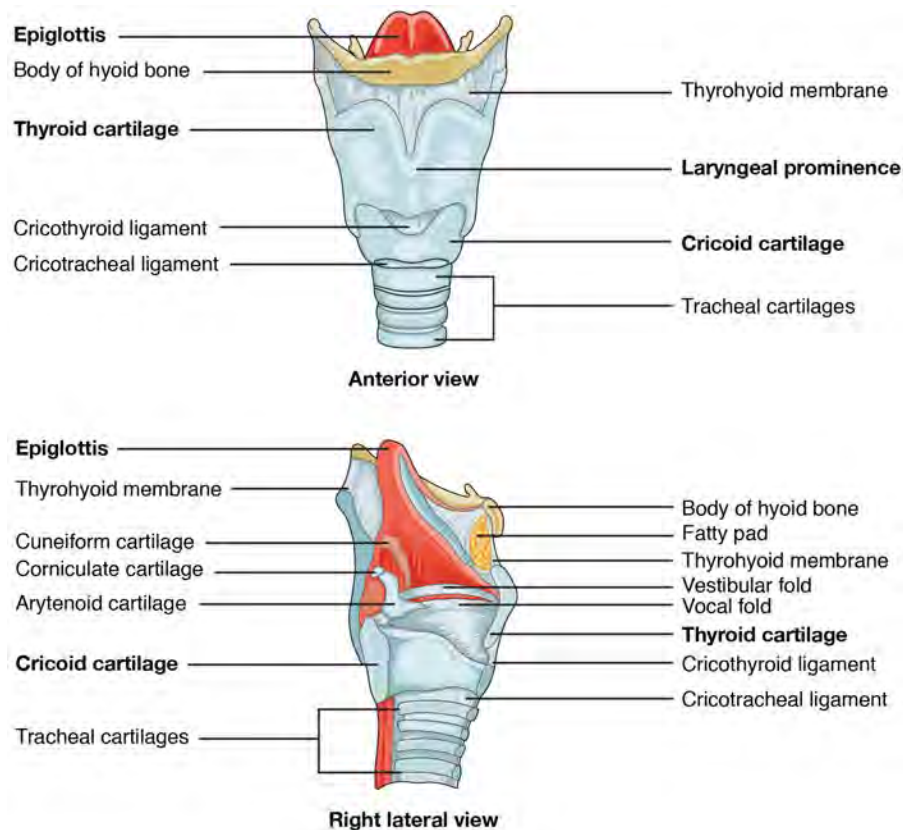
The **oropharynx** is a passageway for both air and food. The oropharynx is bordered superiorly by the nasopharynx and anteriorly by the oral cavity. The **fauces** is the opening at the connection between the oral cavity and the oropharynx. As the nasopharynx becomes the oropharynx, the epithelium changes from pseudostratified ciliated columnar epithelium to stratified squamous epithelium. The oropharynx contains two distinct sets of tonsils, the palatine and lingual tonsils. A **palatine tonsil** is one of a pair of structures located laterally in the oropharynx in the area of the fauces. The **lingual tonsil** is located at the base of the tongue. Similar to the pharyngeal tonsil, the palatine and lingual tonsils are composed of lymphoid tissue, and trap and destroy pathogens entering the body through the oral or nasal cavities.

The **laryngopharynx** is inferior to the oropharynx and posterior to the larynx. It continues the route for ingested material and air until its inferior end, where the digestive and respiratory systems diverge. The stratified squamous epithelium of the oropharynx is continuous with the laryngopharynx. Anteriorly, the laryngopharynx opens into the larynx, whereas posteriorly, it enters the esophagus.

## Larynx

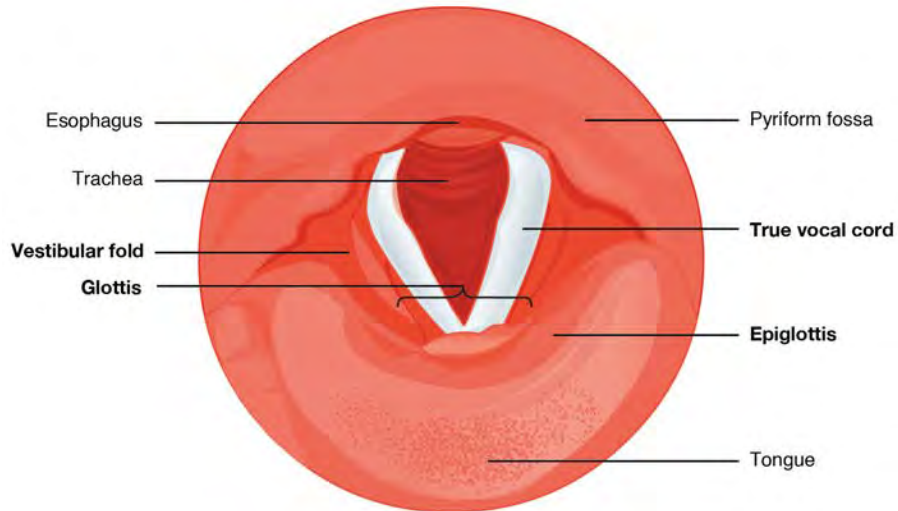
The **larynx** is a cartilaginous structure inferior to the laryngopharynx that connects the pharynx to the trachea and helps regulate the volume of air that enters and leaves the lungs (**Figure 22.7**). The structure of the larynx is formed by several pieces of cartilage. Three large cartilage pieces—the thyroid cartilage (anterior), epiglottis (superior), and cricoid cartilage (inferior)—form the major structure of the larynx. The **thyroid cartilage** is the largest piece of cartilage that makes up the larynx. The thyroid cartilage consists of the **laryngeal prominence**, or “Adam’s apple,” which tends to be more prominent in males. The thick **cricoid cartilage** forms a ring, with a wide posterior region and a thinner anterior region. Three smaller, paired cartilages—the arytenoids, corniculates, and cuneiforms—attach to the epiglottis and the vocal cords and muscle that

help move the vocal cords to produce speech.



**Figure 22.7 Larynx** The larynx extends from the laryngopharynx and the hyoid bone to the trachea.

The **epiglottis**, attached to the thyroid cartilage, is a very flexible piece of elastic cartilage that covers the opening of the trachea (see **Figure 22.4**). When in the “closed” position, the unattached end of the epiglottis rests on the glottis. The **glottis** is composed of the vestibular folds, the true vocal cords, and the space between these folds (**Figure 22.8**). A **vestibular fold**, or false vocal cord, is one of a pair of folded sections of mucous membrane. A **true vocal cord** is one of the white, membranous folds attached by muscle to the thyroid and arytenoid cartilages of the larynx on their outer edges. The inner edges of the true vocal cords are free, allowing oscillation to produce sound. The size of the membranous folds of the true vocal cords differs between individuals, producing voices with different pitch ranges. Folds in males tend to be larger than those in females, which create a deeper voice. The act of swallowing causes the pharynx and larynx to lift upward, allowing the pharynx to expand and the epiglottis of the larynx to swing downward, closing the opening to the trachea. These movements produce a larger area for food to pass through, while preventing food and beverages from entering the trachea.

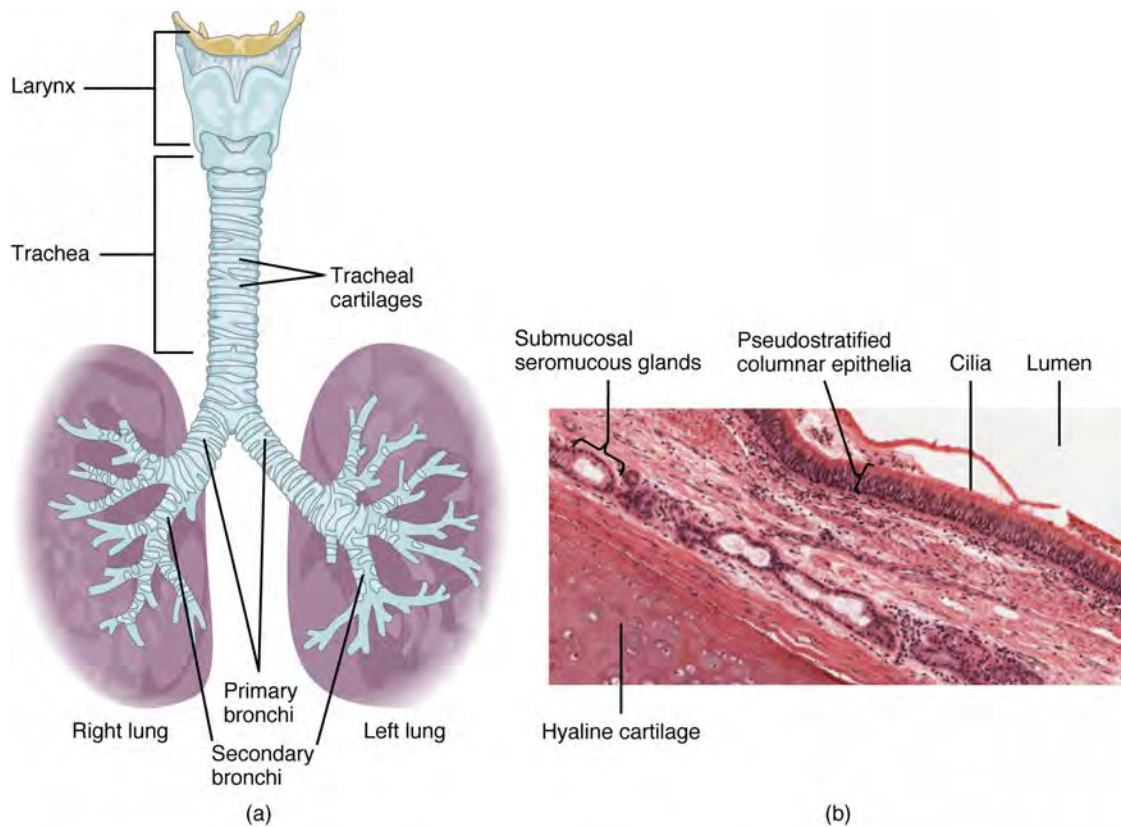


**Figure 22.8 Vocal Cords** The true vocal cords and vestibular folds of the larynx are viewed inferiorly from the laryngopharynx.

Continuous with the laryngopharynx, the superior portion of the larynx is lined with stratified squamous epithelium, transitioning into pseudostratified ciliated columnar epithelium that contains goblet cells. Similar to the nasal cavity and nasopharynx, this specialized epithelium produces mucus to trap debris and pathogens as they enter the trachea. The cilia beat the mucus upward towards the laryngopharynx, where it can be swallowed down the esophagus.

### Trachea

The trachea (windpipe) extends from the larynx toward the lungs (**Figure 22.9a**). The **trachea** is formed by 16 to 20 stacked, C-shaped pieces of hyaline cartilage that are connected by dense connective tissue. The **trachealis muscle** and elastic connective tissue together form the **fibroelastic membrane**, a flexible membrane that closes the posterior surface of the trachea, connecting the C-shaped cartilages. The fibroelastic membrane allows the trachea to stretch and expand slightly during inhalation and exhalation, whereas the rings of cartilage provide structural support and prevent the trachea from collapsing. In addition, the trachealis muscle can be contracted to force air through the trachea during exhalation. The trachea is lined with pseudostratified ciliated columnar epithelium, which is continuous with the larynx. The esophagus borders the trachea posteriorly.



**Figure 22.9 Trachea** (a) The tracheal tube is formed by stacked, C-shaped pieces of hyaline cartilage. (b) The layer visible in this cross-section of tracheal wall tissue between the hyaline cartilage and the lumen of the trachea is the mucosa, which is composed of pseudostratified ciliated columnar epithelium that contains goblet cells. LM  $\times$  1220. (Micrograph provided by the Regents of University of Michigan Medical School  $\copyright$  2012)

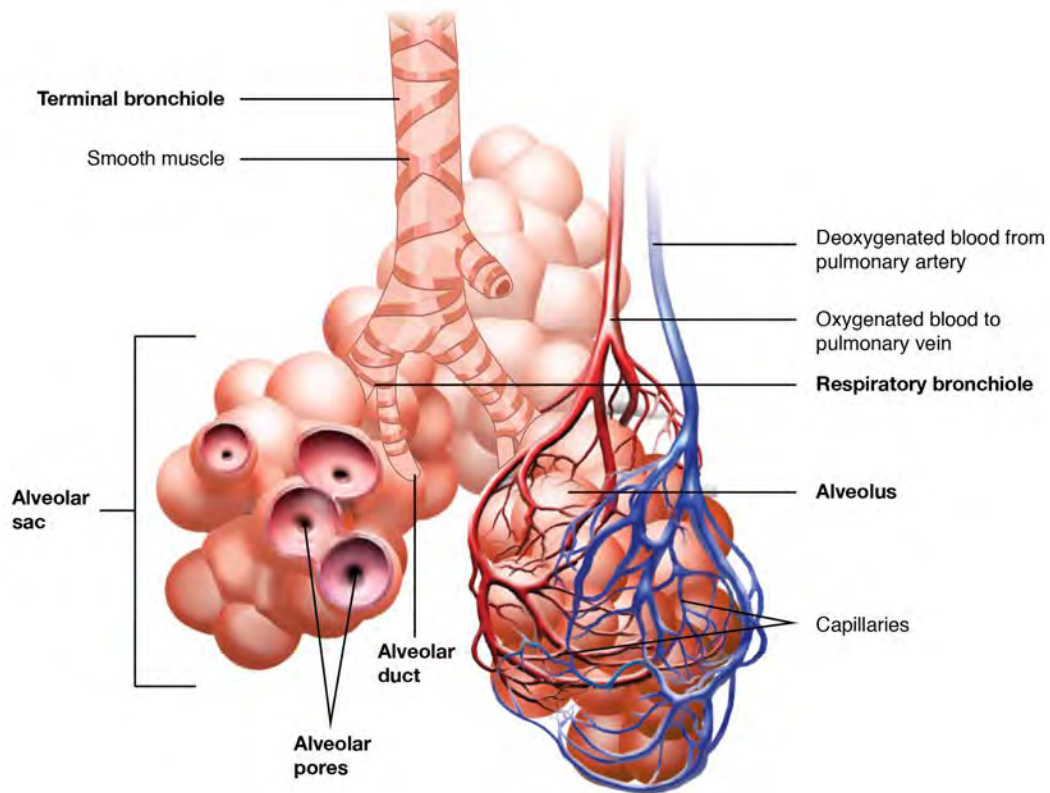
### Bronchial Tree

The trachea branches into the right and left primary **bronchi** at the carina. These bronchi are also lined by pseudostratified ciliated columnar epithelium containing mucus-producing goblet cells (**Figure 22.9b**). The carina is a raised structure that contains specialized nervous tissue that induces violent coughing if a foreign body, such as food, is present. Rings of cartilage, similar to those of the trachea, support the structure of the bronchi and prevent their collapse. The primary bronchi enter the lungs at the hilum, a concave region where blood vessels, lymphatic vessels, and nerves also enter the lungs. The bronchi continue to branch into bronchial a tree. A **bronchial tree** (or respiratory tree) is the collective term used for these multiple-branched bronchi. The main function of the bronchi, like other conducting zone structures, is to provide a passageway for air to move into and out of each lung. In addition, the mucous membrane traps debris and pathogens.

A **bronchiole** branches from the tertiary bronchi. Bronchioles, which are about 1 mm in diameter, further branch until they become the tiny terminal bronchioles, which lead to the structures of gas exchange. There are more than 1000 terminal bronchioles in each lung. The muscular walls of the bronchioles do not contain cartilage like those of the bronchi. This muscular wall can change the size of the tubing to increase or decrease airflow through the tube.

### Respiratory Zone

In contrast to the conducting zone, the respiratory zone includes structures that are directly involved in gas exchange. The respiratory zone begins where the terminal bronchioles join a **respiratory bronchiole**, the smallest type of bronchiole (**Figure 22.10**), which then leads to an alveolar duct, opening into a cluster of alveoli.

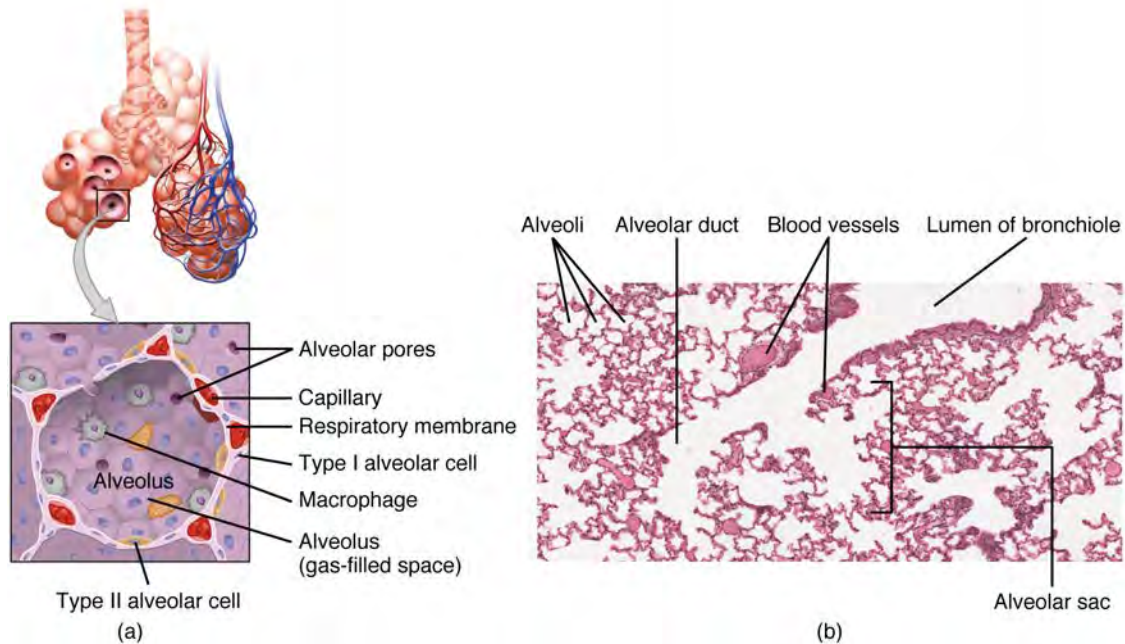


**Figure 22.10 Respiratory Zone** Bronchioles lead to alveolar sacs in the respiratory zone, where gas exchange occurs.

### Alveoli

An **alveolar duct** is a tube composed of smooth muscle and connective tissue, which opens into a cluster of alveoli. An **alveolus** is one of the many small, grape-like sacs that are attached to the alveolar ducts.

An **alveolar sac** is a cluster of many individual alveoli that are responsible for gas exchange. An alveolus is approximately 200  $\mu\text{m}$  in diameter with elastic walls that allow the alveolus to stretch during air intake, which greatly increases the surface area available for gas exchange. Alveoli are connected to their neighbors by **alveolar pores**, which help maintain equal air pressure throughout the alveoli and lung (**Figure 22.11**).



**Figure 22.11 Structures of the Respiratory Zone** (a) The alveolus is responsible for gas exchange. (b) A micrograph shows the alveolar structures within lung tissue. LM  $\times$  178. (Micrograph provided by the Regents of University of Michigan Medical School  $\copyright$  2012)

The alveolar wall consists of three major cell types: type I alveolar cells, type II alveolar cells, and alveolar macrophages. A **type I alveolar cell** is a squamous epithelial cell of the alveoli, which constitute up to 97 percent of the alveolar surface area. These cells are about 25 nm thick and are highly permeable to gases. A **type II alveolar cell** is interspersed among the type I cells and secretes **pulmonary surfactant**, a substance composed of phospholipids and proteins that reduces the surface tension of the alveoli. Roaming around the alveolar wall is the **alveolar macrophage**, a phagocytic cell of the immune system that removes debris and pathogens that have reached the alveoli.

The simple squamous epithelium formed by type I alveolar cells is attached to a thin, elastic basement membrane. This epithelium is extremely thin and borders the endothelial membrane of capillaries. Taken together, the alveoli and capillary membranes form a **respiratory membrane** that is approximately 0.5 mm thick. The respiratory membrane allows gases to cross by simple diffusion, allowing oxygen to be picked up by the blood for transport and  $\text{CO}_2$  to be released into the air of the alveoli.

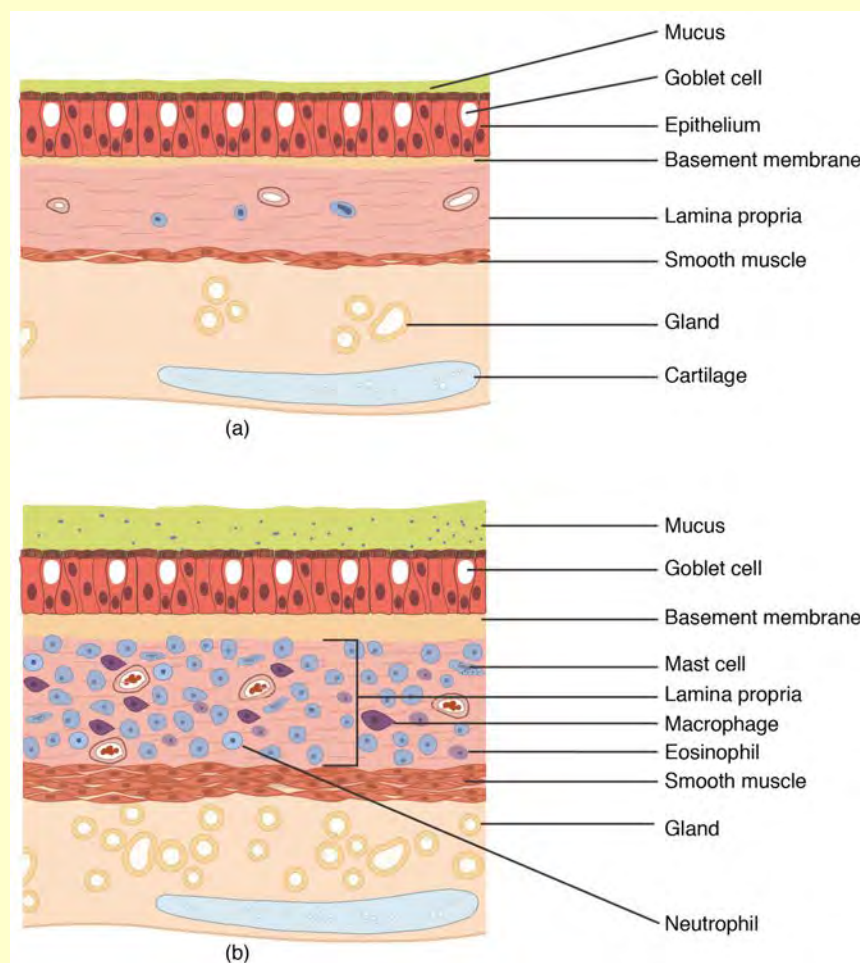
# Diseases OF THE...

## Respiratory System: Asthma

Asthma is a common condition that affects the lungs in both adults and children. Approximately 8.2 percent of adults (18.7 million) and 9.4 percent of children (7 million) in the United States suffer from asthma. In addition, asthma is the most frequent cause of hospitalization in children.

Asthma is a chronic disease characterized by inflammation and edema of the airway, and bronchospasms (that is, constriction of the bronchioles), which can inhibit air from entering the lungs. In addition, excessive mucus secretion can occur, which further contributes to airway occlusion (**Figure 22.12**). Cells of the immune system, such as eosinophils and mononuclear cells, may also be involved in infiltrating the walls of the bronchi and bronchioles.

Bronchospasms occur periodically and lead to an “asthma attack.” An attack may be triggered by environmental factors such as dust, pollen, pet hair, or dander, changes in the weather, mold, tobacco smoke, and respiratory infections, or by exercise and stress.



**Figure 22.12 Normal and Bronchial Asthma Tissues** (a) Normal lung tissue does not have the characteristics of lung tissue during (b) an asthma attack, which include thickened mucosa, increased mucus-producing goblet cells, and eosinophil infiltrates.

Symptoms of an asthma attack involve coughing, shortness of breath, wheezing, and tightness of the chest. Symptoms of a severe asthma attack that requires immediate medical attention would include difficulty breathing that results in blue (cyanotic) lips or face, confusion, drowsiness, a rapid pulse, sweating, and severe anxiety. The severity of the

condition, frequency of attacks, and identified triggers influence the type of medication that an individual may require. Longer-term treatments are used for those with more severe asthma. Short-term, fast-acting drugs that are used to treat an asthma attack are typically administered via an inhaler. For young children or individuals who have difficulty using an inhaler, asthma medications can be administered via a nebulizer.

In many cases, the underlying cause of the condition is unknown. However, recent research has demonstrated that certain viruses, such as human rhinovirus C (HRVC), and the bacteria *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* that are contracted in infancy or early childhood, may contribute to the development of many cases of asthma.

## Interactive LINK



Visit this [site \(http://openstaxcollege.org/l/asthma\)](http://openstaxcollege.org/l/asthma) to learn more about what happens during an asthma attack. What are the three changes that occur inside the airways during an asthma attack?

## 22.2 | The Lungs

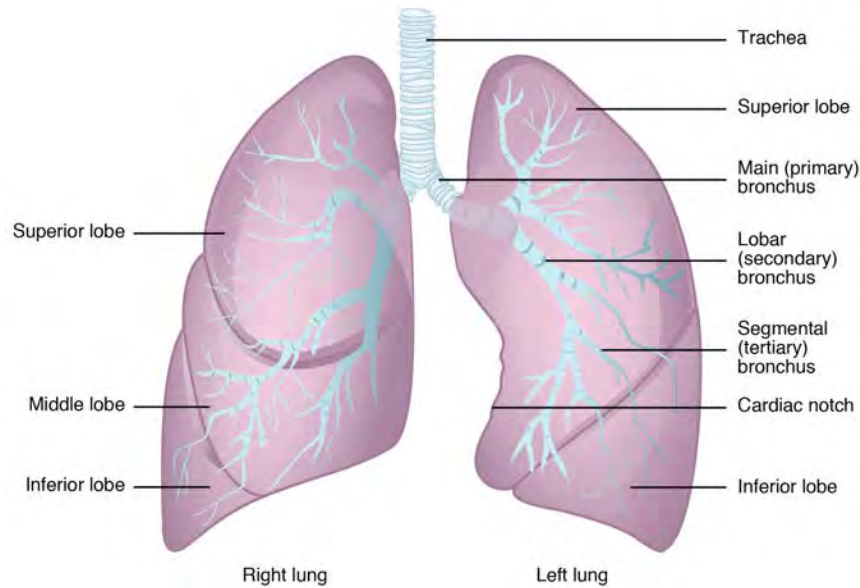
By the end of this section, you will be able to:

- Describe the overall function of the lung
- Summarize the blood flow pattern associated with the lungs
- Outline the anatomy of the blood supply to the lungs
- Describe the pleura of the lungs and their function

A major organ of the respiratory system, each **lung** houses structures of both the conducting and respiratory zones. The main function of the lungs is to perform the exchange of oxygen and carbon dioxide with air from the atmosphere. To this end, the lungs exchange respiratory gases across a very large epithelial surface area—about 70 square meters—that is highly permeable to gases.

### Gross Anatomy of the Lungs

The lungs are pyramid-shaped, paired organs that are connected to the trachea by the right and left bronchi; on the inferior surface, the lungs are bordered by the diaphragm. The diaphragm is the flat, dome-shaped muscle located at the base of the lungs and thoracic cavity. The lungs are enclosed by the pleurae, which are attached to the mediastinum. The right lung is shorter and wider than the left lung, and the left lung occupies a smaller volume than the right. The **cardiac notch** is an indentation on the surface of the left lung, and it allows space for the heart (**Figure 22.13**). The apex of the lung is the superior region, whereas the base is the opposite region near the diaphragm. The costal surface of the lung borders the ribs. The mediastinal surface faces the midline.



**Figure 22.13 Gross Anatomy of the Lungs**

Each lung is composed of smaller units called lobes. Fissures separate these lobes from each other. The right lung consists of three lobes: the superior, middle, and inferior lobes. The left lung consists of two lobes: the superior and inferior lobes. A bronchopulmonary segment is a division of a lobe, and each lobe houses multiple bronchopulmonary segments. Each segment receives air from its own tertiary bronchus and is supplied with blood by its own artery. Some diseases of the lungs typically affect one or more bronchopulmonary segments, and in some cases, the diseased segments can be surgically removed with little influence on neighboring segments. A pulmonary lobule is a subdivision formed as the bronchi branch into bronchioles. Each lobule receives its own large bronchiole that has multiple branches. An interlobular septum is a wall, composed of connective tissue, which separates lobules from one another.

## Blood Supply and Nervous Innervation of the Lungs

The blood supply of the lungs plays an important role in gas exchange and serves as a transport system for gases throughout the body. In addition, innervation by both the parasympathetic and sympathetic nervous systems provides an important level of control through dilation and constriction of the airway.

### Blood Supply

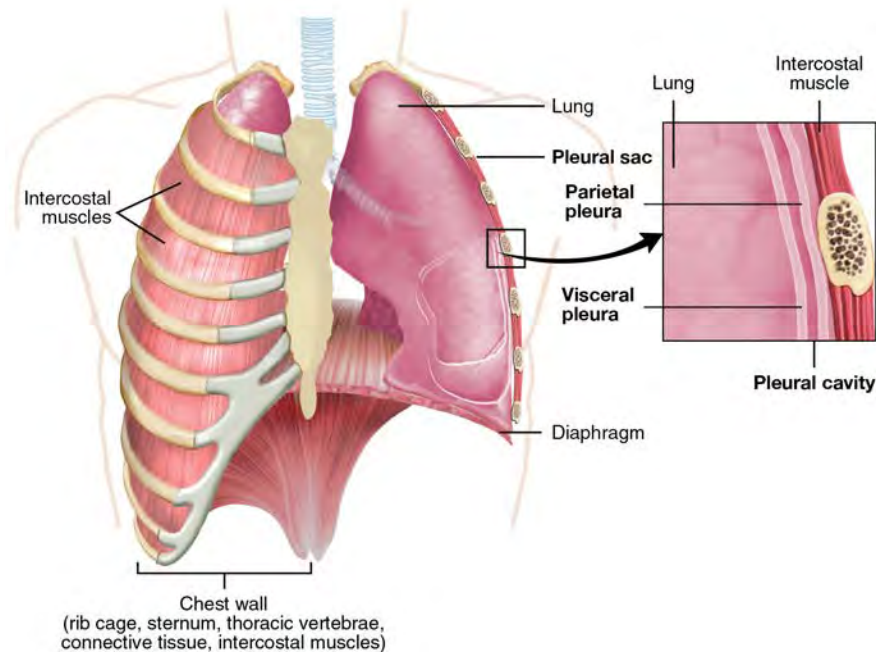
The major function of the lungs is to perform gas exchange, which requires blood from the pulmonary circulation. This blood supply contains deoxygenated blood and travels to the lungs where erythrocytes, also known as red blood cells, pick up oxygen to be transported to tissues throughout the body. The **pulmonary artery** is an artery that arises from the pulmonary trunk and carries deoxygenated, arterial blood to the alveoli. The pulmonary artery branches multiple times as it follows the bronchi, and each branch becomes progressively smaller in diameter. One arteriole and an accompanying venule supply and drain one pulmonary lobule. As they near the alveoli, the pulmonary arteries become the pulmonary capillary network. The pulmonary capillary network consists of tiny vessels with very thin walls that lack smooth muscle fibers. The capillaries branch and follow the bronchioles and structure of the alveoli. It is at this point that the capillary wall meets the alveolar wall, creating the respiratory membrane. Once the blood is oxygenated, it drains from the alveoli by way of multiple pulmonary veins, which exit the lungs through the **hilum**.

### Nervous Innervation

Dilation and constriction of the airway are achieved through nervous control by the parasympathetic and sympathetic nervous systems. The parasympathetic system causes **bronchoconstriction**, whereas the sympathetic nervous system stimulates **bronchodilation**. Reflexes such as coughing, and the ability of the lungs to regulate oxygen and carbon dioxide levels, also result from this autonomic nervous system control. Sensory nerve fibers arise from the vagus nerve, and from the second to fifth thoracic ganglia. The **pulmonary plexus** is a region on the lung root formed by the entrance of the nerves at the hilum. The nerves then follow the bronchi in the lungs and branch to innervate muscle fibers, glands, and blood vessels.

## Pleura of the Lungs

Each lung is enclosed within a cavity that is surrounded by the pleura. The pleura (plural = pleurae) is a serous membrane that surrounds the lung. The right and left pleurae, which enclose the right and left lungs, respectively, are separated by the mediastinum. The pleurae consist of two layers. The **visceral pleura** is the layer that is superficial to the lungs, and extends into and lines the lung fissures (**Figure 22.14**). In contrast, the **parietal pleura** is the outer layer that connects to the thoracic wall, the mediastinum, and the diaphragm. The visceral and parietal pleurae connect to each other at the hilum. The **pleural cavity** is the space between the visceral and parietal layers.



**Figure 22.14 Parietal and Visceral Pleurae of the Lungs**

The pleurae perform two major functions: They produce pleural fluid and create cavities that separate the major organs. **Pleural fluid** is secreted by mesothelial cells from both pleural layers and acts to lubricate their surfaces. This lubrication reduces friction between the two layers to prevent trauma during breathing, and creates surface tension that helps maintain the position of the lungs against the thoracic wall. This adhesive characteristic of the pleural fluid causes the lungs to enlarge when the thoracic wall expands during ventilation, allowing the lungs to fill with air. The pleurae also create a division between major organs that prevents interference due to the movement of the organs, while preventing the spread of infection.

## Everyday CONNECTION

### The Effects of Second-Hand Tobacco Smoke

The burning of a tobacco cigarette creates multiple chemical compounds that are released through mainstream smoke, which is inhaled by the smoker, and through sidestream smoke, which is the smoke that is given off by the burning cigarette. Second-hand smoke, which is a combination of sidestream smoke and the mainstream smoke that is exhaled by the smoker, has been demonstrated by numerous scientific studies to cause disease. At least 40 chemicals in sidestream smoke have been identified that negatively impact human health, leading to the development of cancer or other conditions, such as immune system dysfunction, liver toxicity, cardiac arrhythmias, pulmonary edema, and neurological dysfunction. Furthermore, second-hand smoke has been found to harbor at least 250 compounds that are known to be toxic, carcinogenic, or both. Some major classes of carcinogens in second-hand smoke are polycyclic aromatic hydrocarbons (PAHs), N-nitrosamines, aromatic amines, formaldehyde, and acetaldehyde.

Tobacco and second-hand smoke are considered to be carcinogenic. Exposure to second-hand smoke can cause lung cancer in individuals who are not tobacco users themselves. It is estimated that the risk of developing lung cancer is increased by up to 30 percent in nonsmokers who live with an individual who smokes in the house, as compared to nonsmokers who are not regularly exposed to second-hand smoke. Children are especially affected by second-hand smoke. Children who live with an individual who smokes inside the home have a larger number of lower respiratory infections, which are associated with hospitalizations, and higher risk of sudden infant death syndrome (SIDS). Second-hand smoke in the home has also been linked to a greater number of ear infections in children, as well as worsening symptoms of asthma.

## 22.3 | The Process of Breathing

By the end of this section, you will be able to:

- Describe the mechanisms that drive breathing
- Discuss how pressure, volume, and resistance are related
- List the steps involved in pulmonary ventilation
- Discuss the physical factors related to breathing
- Discuss the meaning of respiratory volume and capacities
- Define respiratory rate
- Outline the mechanisms behind the control of breathing
- Describe the respiratory centers of the medulla oblongata
- Describe the respiratory centers of the pons
- Discuss factors that can influence the respiratory rate

**Pulmonary ventilation** is the act of breathing, which can be described as the movement of air into and out of the lungs. The major mechanisms that drive pulmonary ventilation are atmospheric pressure ( $P_{\text{atm}}$ ); the air pressure within the alveoli, called intra-alveolar pressure ( $P_{\text{alv}}$ ); and the pressure within the pleural cavity, called intrapleural pressure ( $P_{\text{ip}}$ ).

### Mechanisms of Breathing

The intra-alveolar and intrapleural pressures are dependent on certain physical features of the lung. However, the ability to breathe—to have air enter the lungs during inspiration and air leave the lungs during expiration—is dependent on the air pressure of the atmosphere and the air pressure within the lungs.

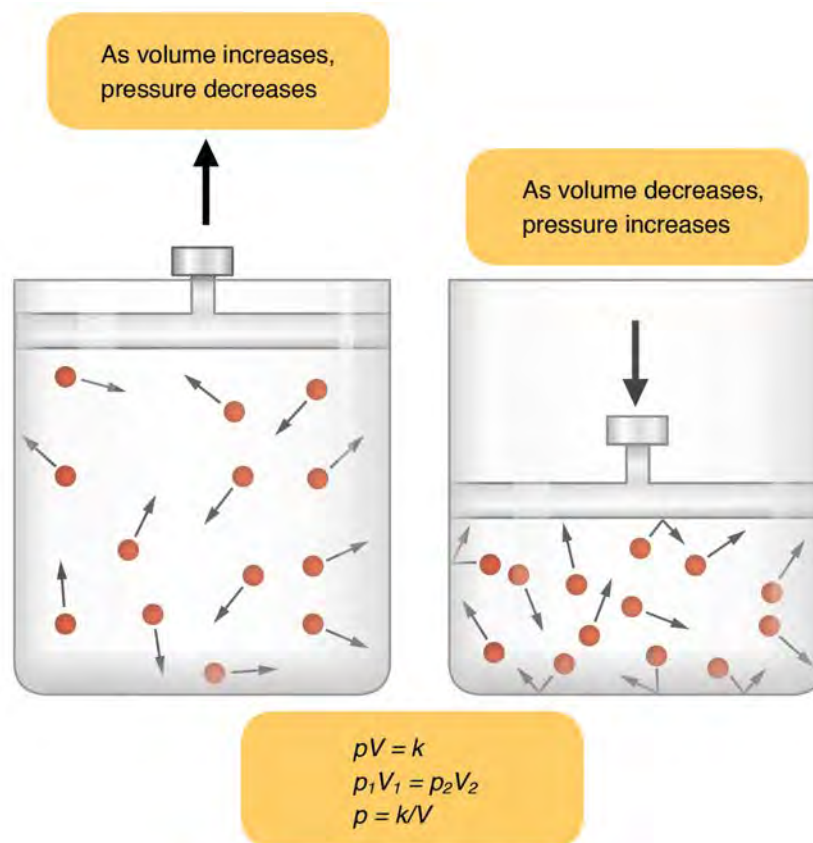
#### Pressure Relationships

Inspiration (or inhalation) and expiration (or exhalation) are dependent on the differences in pressure between the atmosphere and the lungs. In a gas, pressure is a force created by the movement of gas molecules that are confined. For example, a certain number of gas molecules in a two-liter container has more room than the same number of gas molecules

in a one-liter container (**Figure 22.15**). In this case, the force exerted by the movement of the gas molecules against the walls of the two-liter container is lower than the force exerted by the gas molecules in the one-liter container. Therefore, the pressure is lower in the two-liter container and higher in the one-liter container. At a constant temperature, changing the volume occupied by the gas changes the pressure, as does changing the number of gas molecules. **Boyle's law** describes the relationship between volume and pressure in a gas at a constant temperature. Boyle discovered that the pressure of a gas is inversely proportional to its volume: If volume increases, pressure decreases. Likewise, if volume decreases, pressure increases. Pressure and volume are inversely related ( $P = k/V$ ). Therefore, the pressure in the one-liter container (one-half the volume of the two-liter container) would be twice the pressure in the two-liter container. Boyle's law is expressed by the following formula:

$$P_1 V_1 = P_2 V_2$$

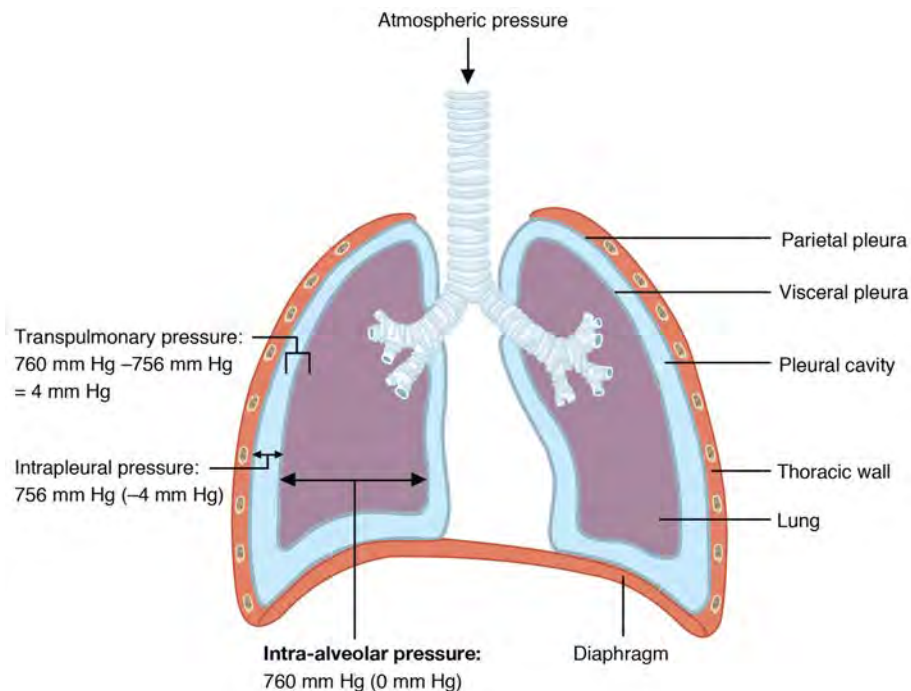
In this formula,  $P_1$  represents the initial pressure and  $V_1$  represents the initial volume, whereas the final pressure and volume are represented by  $P_2$  and  $V_2$ , respectively. If the two- and one-liter containers were connected by a tube and the volume of one of the containers were changed, then the gases would move from higher pressure (lower volume) to lower pressure (higher volume).



**Figure 22.15 Boyle's Law** In a gas, pressure increases as volume decreases.

Pulmonary ventilation is dependent on three types of pressure: atmospheric, intra-alveolar, and intrapleural. **Atmospheric pressure** is the amount of force that is exerted by gases in the air surrounding any given surface, such as the body. Atmospheric pressure can be expressed in terms of the unit atmosphere, abbreviated atm, or in millimeters of mercury (mm Hg). One atm is equal to 760 mm Hg, which is the atmospheric pressure at sea level. Typically, for respiration, other pressure values are discussed in relation to atmospheric pressure. Therefore, negative pressure is pressure lower than the atmospheric pressure, whereas positive pressure is pressure that is greater than the atmospheric pressure. A pressure that is equal to the atmospheric pressure is expressed as zero.

**Intra-alveolar pressure** (intrapulmonary pressure) is the pressure of the air within the alveoli, which changes during the different phases of breathing (**Figure 22.16**). Because the alveoli are connected to the atmosphere via the tubing of the airways (similar to the two- and one-liter containers in the example above), the intrapulmonary pressure of the alveoli always equalizes with the atmospheric pressure.



**Figure 22.16 Intrapulmonary and Intrapleural Pressure Relationships** Intra-alveolar pressure changes during the different phases of the cycle. It equalizes at 760 mm Hg but does not remain at 760 mm Hg.

**Intrapleural pressure** is the pressure of the air within the pleural cavity, between the visceral and parietal pleurae. Similar to intra-alveolar pressure, intrapleural pressure also changes during the different phases of breathing. However, due to certain characteristics of the lungs, the intrapleural pressure is always lower than, or negative to, the intra-alveolar pressure (and therefore also to atmospheric pressure). Although it fluctuates during inspiration and expiration, intrapleural pressure remains approximately  $-4$  mm Hg throughout the breathing cycle.

Competing forces within the thorax cause the formation of the negative intrapleural pressure. One of these forces relates to the elasticity of the lungs themselves—elastic tissue pulls the lungs inward, away from the thoracic wall. Surface tension of alveolar fluid, which is mostly water, also creates an inward pull of the lung tissue. This inward tension from the lungs is countered by opposing forces from the pleural fluid and thoracic wall. Surface tension within the pleural cavity pulls the lungs outward. Too much or too little pleural fluid would hinder the creation of the negative intrapleural pressure; therefore, the level must be closely monitored by the mesothelial cells and drained by the lymphatic system. Since the parietal pleura is attached to the thoracic wall, the natural elasticity of the chest wall opposes the inward pull of the lungs. Ultimately, the outward pull is slightly greater than the inward pull, creating the  $-4$  mm Hg intrapleural pressure relative to the intra-alveolar pressure. **Transpulmonary pressure** is the difference between the intrapleural and intra-alveolar pressures, and it determines the size of the lungs. A higher transpulmonary pressure corresponds to a larger lung.

### Physical Factors Affecting Ventilation

In addition to the differences in pressures, breathing is also dependent upon the contraction and relaxation of muscle fibers of both the diaphragm and thorax. The lungs themselves are passive during breathing, meaning they are not involved in creating the movement that helps inspiration and expiration. This is because of the adhesive nature of the pleural fluid, which allows the lungs to be pulled outward when the thoracic wall moves during inspiration. The recoil of the thoracic wall during expiration causes compression of the lungs. Contraction and relaxation of the diaphragm and intercostals muscles (found between the ribs) cause most of the pressure changes that result in inspiration and expiration. These muscle movements and subsequent pressure changes cause air to either rush in or be forced out of the lungs.

Other characteristics of the lungs influence the effort that must be expended to ventilate. Resistance is a force that slows motion, in this case, the flow of gases. The size of the airway is the primary factor affecting resistance. A small tubular diameter forces air through a smaller space, causing more collisions of air molecules with the walls of the airways. The following formula helps to describe the relationship between airway resistance and pressure changes:

$$F = \Delta P / R$$

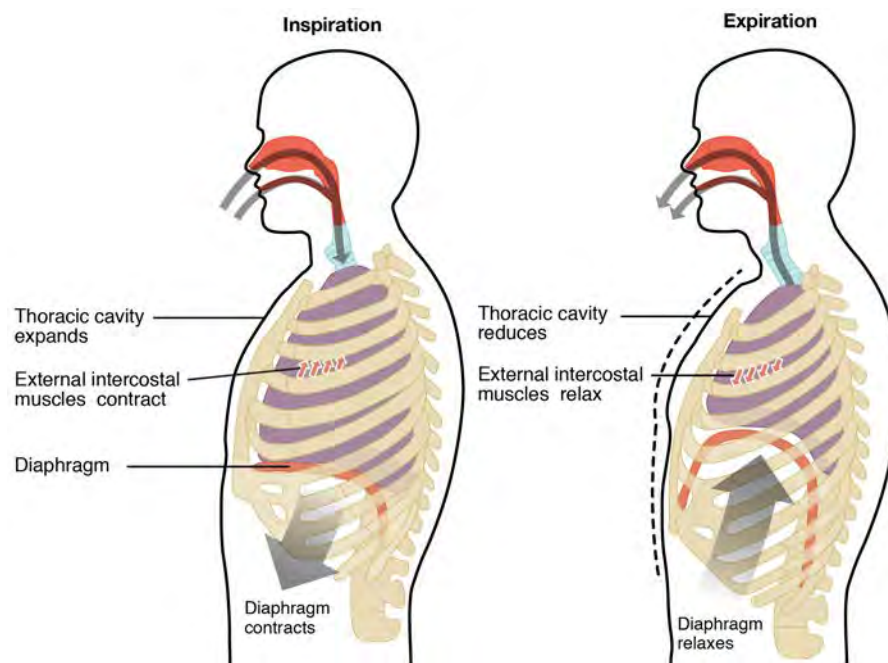
As noted earlier, there is surface tension within the alveoli caused by water present in the lining of the alveoli. This surface tension tends to inhibit expansion of the alveoli. However, pulmonary surfactant secreted by type II alveolar cells mixes with that water and helps reduce this surface tension. Without pulmonary surfactant, the alveoli would collapse during expiration.

**Thoracic wall compliance** is the ability of the thoracic wall to stretch while under pressure. This can also affect the effort expended in the process of breathing. In order for inspiration to occur, the thoracic cavity must expand. The expansion of the thoracic cavity directly influences the capacity of the lungs to expand. If the tissues of the thoracic wall are not very compliant, it will be difficult to expand the thorax to increase the size of the lungs.

## Pulmonary Ventilation

The difference in pressures drives pulmonary ventilation because air flows down a pressure gradient, that is, air flows from an area of higher pressure to an area of lower pressure. Air flows into the lungs largely due to a difference in pressure; atmospheric pressure is greater than intra-alveolar pressure, and intra-alveolar pressure is greater than intrapleural pressure. Air flows out of the lungs during expiration based on the same principle; pressure within the lungs becomes greater than the atmospheric pressure.

Pulmonary ventilation comprises two major steps: inspiration and expiration. **Inspiration** is the process that causes air to enter the lungs, and **expiration** is the process that causes air to leave the lungs (Figure 22.17). A **respiratory cycle** is one sequence of inspiration and expiration. In general, two muscle groups are used during normal inspiration: the diaphragm and the external intercostal muscles. Additional muscles can be used if a bigger breath is required. When the diaphragm contracts, it moves inferiorly toward the abdominal cavity, creating a larger thoracic cavity and more space for the lungs. Contraction of the external intercostal muscles moves the ribs upward and outward, causing the rib cage to expand, which increases the volume of the thoracic cavity. Due to the adhesive force of the pleural fluid, the expansion of the thoracic cavity forces the lungs to stretch and expand as well. This increase in volume leads to a decrease in intra-alveolar pressure, creating a pressure lower than atmospheric pressure. As a result, a pressure gradient is created that drives air into the lungs.



**Figure 22.17 Inspiration and Expiration** Inspiration and expiration occur due to the expansion and contraction of the thoracic cavity, respectively.

The process of normal expiration is passive, meaning that energy is not required to push air out of the lungs. Instead, the elasticity of the lung tissue causes the lung to recoil, as the diaphragm and intercostal muscles relax following inspiration. In turn, the thoracic cavity and lungs decrease in volume, causing an increase in intrapulmonary pressure. The intrapulmonary pressure rises above atmospheric pressure, creating a pressure gradient that causes air to leave the lungs.

There are different types, or modes, of breathing that require a slightly different process to allow inspiration and expiration. **Quiet breathing**, also known as eupnea, is a mode of breathing that occurs at rest and does not require the cognitive thought

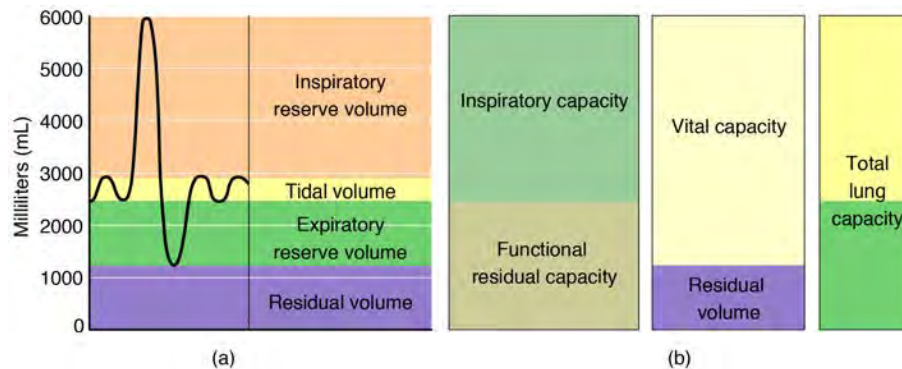
of the individual. During quiet breathing, the diaphragm and external intercostals must contract.

A deep breath, called diaphragmatic breathing, requires the diaphragm to contract. As the diaphragm relaxes, air passively leaves the lungs. A shallow breath, called costal breathing, requires contraction of the intercostal muscles. As the intercostal muscles relax, air passively leaves the lungs.

In contrast, **forced breathing**, also known as hyperpnea, is a mode of breathing that can occur during exercise or actions that require the active manipulation of breathing, such as singing. During forced breathing, inspiration and expiration both occur due to muscle contractions. In addition to the contraction of the diaphragm and intercostal muscles, other accessory muscles must also contract. During forced inspiration, muscles of the neck, including the scalenes, contract and lift the thoracic wall, increasing lung volume. During forced expiration, accessory muscles of the abdomen, including the obliques, contract, forcing abdominal organs upward against the diaphragm. This helps to push the diaphragm further into the thorax, pushing more air out. In addition, accessory muscles (primarily the internal intercostals) help to compress the rib cage, which also reduces the volume of the thoracic cavity.

## Respiratory Volumes and Capacities

**Respiratory volume** is the term used for various volumes of air moved by or associated with the lungs at a given point in the respiratory cycle. There are four major types of respiratory volumes: tidal, residual, inspiratory reserve, and expiratory reserve (Figure 22.18). **Tidal volume (TV)** is the amount of air that normally enters the lungs during quiet breathing, which is about 500 milliliters. **Expiratory reserve volume (ERV)** is the amount of air you can forcefully exhale past a normal tidal expiration, up to 1200 milliliters for men. **Inspiratory reserve volume (IRV)** is produced by a deep inhalation, past a tidal inspiration. This is the extra volume that can be brought into the lungs during a forced inspiration. **Residual volume (RV)** is the air left in the lungs if you exhale as much air as possible. The residual volume makes breathing easier by preventing the alveoli from collapsing. Respiratory volume is dependent on a variety of factors, and measuring the different types of respiratory volumes can provide important clues about a person's respiratory health (Figure 22.19).



**Figure 22.18 Respiratory Volumes and Capacities** These two graphs show (a) respiratory volumes and (b) the combination of volumes that results in respiratory capacity.

Pulmonary function test	Instrument	Measures	Function
Spirometry	Spirometer	Forced vital capacity (FVC)	Volume of air that is exhaled after maximum inhalation
		Forced expiratory volume (FEV)	Volume of air exhaled during one forced breath
		Forced expiratory flow, 25–75 percent	Air flow in the middle of exhalation
		Peak expiratory flow (PEF)	Rate of exhalation
		Maximum voluntary ventilation (MVV)	Volume of air that can be inspired and expired in 1 minute
		Slow vital capacity (SVC)	Volume of air that can be slowly exhaled after inhaling past the tidal volume
		Total lung capacity (TLC)	Volume of air in the lungs after maximum inhalation
		Functional residual capacity (FRC)	Volume of air left in the lungs after normal expiration
		Residual volume (RV)	Volume of air in the lungs after maximum exhalation
		Total lung capacity (TLC)	Maximum volume of air that the lungs can hold
		Expiratory reserve volume (ERV)	The volume of air that can be exhaled beyond normal exhalation
Gas diffusion	Blood gas analyzer	Arterial blood gases	Concentration of oxygen and carbon dioxide in the blood

**Figure 22.19 Pulmonary Function Testing**

Respiratory capacity is the combination of two or more selected volumes, which further describes the amount of air in the lungs during a given time. For example, **total lung capacity (TLC)** is the sum of all of the lung volumes (TV, ERV, IRV, and RV), which represents the total amount of air a person can hold in the lungs after a forceful inhalation. TLC is about 6000 mL air for men, and about 4200 mL for women. **Vital capacity (VC)** is the amount of air a person can move into or out of his or her lungs, and is the sum of all of the volumes except residual volume (TV, ERV, and IRV), which is between 4000 and 5000 milliliters. **Inspiratory capacity (IC)** is the maximum amount of air that can be inhaled past a normal tidal expiration, is the sum of the tidal volume and inspiratory reserve volume. On the other hand, the **functional residual capacity (FRC)** is the amount of air that remains in the lung after a normal tidal expiration; it is the sum of expiratory reserve volume and residual volume (see **Figure 22.18**).



Watch this **video** (<http://openstaxcollege.org/l/spirometers>) to learn more about lung volumes and spirometers. Explain how spirometry test results can be used to diagnose respiratory diseases or determine the effectiveness of disease treatment.

In addition to the air that creates respiratory volumes, the respiratory system also contains **anatomical dead space**, which is air that is present in the airway that never reaches the alveoli and therefore never participates in gas exchange. **Alveolar dead space** involves air found within alveoli that are unable to function, such as those affected by disease or abnormal

blood flow. **Total dead space** is the anatomical dead space and alveolar dead space together, and represents all of the air in the respiratory system that is not being used in the gas exchange process.

## Respiratory Rate and Control of Ventilation

Breathing usually occurs without thought, although at times you can consciously control it, such as when you swim under water, sing a song, or blow bubbles. The **respiratory rate** is the total number of breaths, or respiratory cycles, that occur each minute. Respiratory rate can be an important indicator of disease, as the rate may increase or decrease during an illness or in a disease condition. The respiratory rate is controlled by the respiratory center located within the medulla oblongata in the brain, which responds primarily to changes in carbon dioxide, oxygen, and pH levels in the blood.

The normal respiratory rate of a child decreases from birth to adolescence. A child under 1 year of age has a normal respiratory rate between 30 and 60 breaths per minute, but by the time a child is about 10 years old, the normal rate is closer to 18 to 30. By adolescence, the normal respiratory rate is similar to that of adults, 12 to 18 breaths per minute.

### Ventilation Control Centers

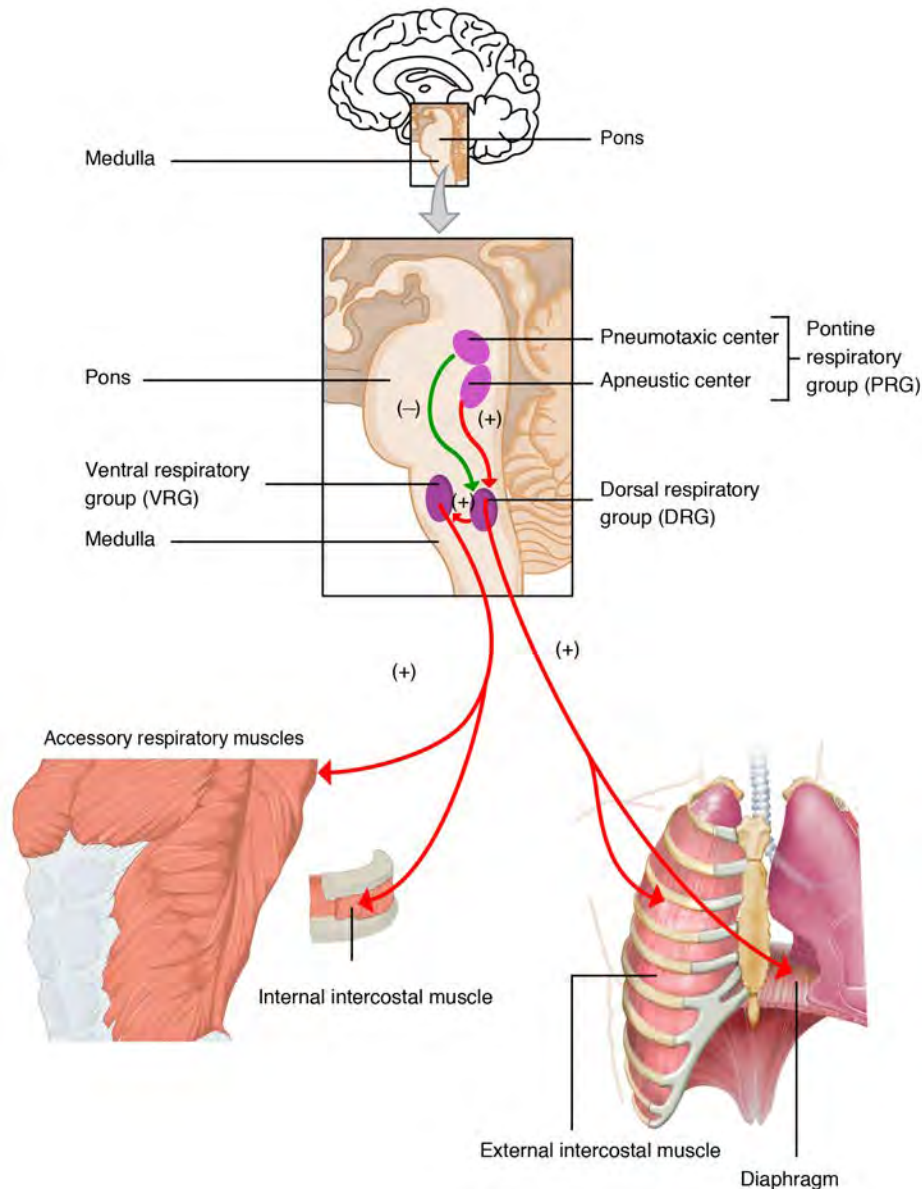
The control of ventilation is a complex interplay of multiple regions in the brain that signal the muscles used in pulmonary ventilation to contract (**Table 22.1**). The result is typically a rhythmic, consistent ventilation rate that provides the body with sufficient amounts of oxygen, while adequately removing carbon dioxide.

### Summary of Ventilation Regulation

System component	Function
Medullary respiratory center	Sets the basic rhythm of breathing
Ventral respiratory group (VRG)	Generates the breathing rhythm and integrates data coming into the medulla
Dorsal respiratory group (DRG)	Integrates input from the stretch receptors and the chemoreceptors in the periphery
Pontine respiratory group (PRG)	Influences and modifies the medulla oblongata's functions
Aortic body	Monitors blood PCO <sub>2</sub> , PO <sub>2</sub> , and pH
Carotid body	Monitors blood PCO <sub>2</sub> , PO <sub>2</sub> , and pH
Hypothalamus	Monitors emotional state and body temperature
Cortical areas of the brain	Control voluntary breathing
Proprioceptors	Send impulses regarding joint and muscle movements
Pulmonary irritant reflexes	Protect the respiratory zones of the system from foreign material
Inflation reflex	Protects the lungs from over-inflating

**Table 22.1**

Neurons that innervate the muscles of the respiratory system are responsible for controlling and regulating pulmonary ventilation. The major brain centers involved in pulmonary ventilation are the medulla oblongata and the pontine respiratory group (**Figure 22.20**).



**Figure 22.20 Respiratory Centers of the Brain**

The medulla oblongata contains the **dorsal respiratory group (DRG)** and the **ventral respiratory group (VRG)**. The DRG is involved in maintaining a constant breathing rhythm by stimulating the diaphragm and intercostal muscles to contract, resulting in inspiration. When activity in the DRG ceases, it no longer stimulates the diaphragm and intercostals to contract, allowing them to relax, resulting in expiration. The VRG is involved in forced breathing, as the neurons in the VRG stimulate the accessory muscles involved in forced breathing to contract, resulting in forced inspiration. The VRG also stimulates the accessory muscles involved in forced expiration to contract.

The second respiratory center of the brain is located within the pons, called the pontine respiratory group, and consists of the apneustic and pneumotaxic centers. The **apneustic center** is a double cluster of neuronal cell bodies that stimulate neurons in the DRG, controlling the depth of inspiration, particularly for deep breathing. The **pneumotaxic center** is a network of neurons that inhibits the activity of neurons in the DRG, allowing relaxation after inspiration, and thus controlling the overall rate.

### Factors That Affect the Rate and Depth of Respiration

The respiratory rate and the depth of inspiration are regulated by the medulla oblongata and pons; however, these regions of the brain do so in response to systemic stimuli. It is a dose-response, negative-feedback relationship in which the greater

the stimulus, the greater the response. Thus, increasing stimuli results in forced breathing. Multiple systemic factors are involved in stimulating the brain to produce pulmonary ventilation.

The major factor that stimulates the medulla oblongata and pons to produce respiration is surprisingly not oxygen concentration, but rather the concentration of carbon dioxide in the blood. As you recall, carbon dioxide is a waste product of cellular respiration and can be toxic. Concentrations of chemicals are sensed by chemoreceptors. A **central chemoreceptor** is one of the specialized receptors that are located in the brain and brainstem, whereas a **peripheral chemoreceptor** is one of the specialized receptors located in the carotid arteries and aortic arch. Concentration changes in certain substances, such as carbon dioxide or hydrogen ions, stimulate these receptors, which in turn signal the respiration centers of the brain. In the case of carbon dioxide, as the concentration of CO<sub>2</sub> in the blood increases, it readily diffuses across the blood-brain barrier, where it collects in the extracellular fluid. As will be explained in more detail later, increased carbon dioxide levels lead to increased levels of hydrogen ions, decreasing pH. The increase in hydrogen ions in the brain triggers the central chemoreceptors to stimulate the respiratory centers to initiate contraction of the diaphragm and intercostal muscles. As a result, the rate and depth of respiration increase, allowing more carbon dioxide to be expelled, which brings more air into and out of the lungs promoting a reduction in the blood levels of carbon dioxide, and therefore hydrogen ions, in the blood. In contrast, low levels of carbon dioxide in the blood cause low levels of hydrogen ions in the brain, leading to a decrease in the rate and depth of pulmonary ventilation, producing shallow, slow breathing.

Another factor involved in influencing the respiratory activity of the brain is systemic arterial concentrations of hydrogen ions. Increasing carbon dioxide levels can lead to increased H<sup>+</sup> levels, as mentioned above, as well as other metabolic activities, such as lactic acid accumulation after strenuous exercise. Peripheral chemoreceptors of the aortic arch and carotid arteries sense arterial levels of hydrogen ions. When peripheral chemoreceptors sense decreasing, or more acidic, pH levels, they stimulate an increase in ventilation to remove carbon dioxide from the blood at a quicker rate. Removal of carbon dioxide from the blood helps to reduce hydrogen ions, thus increasing systemic pH.

Blood levels of oxygen are also important in influencing respiratory rate. The peripheral chemoreceptors are responsible for sensing large changes in blood oxygen levels. If blood oxygen levels become quite low—about 60 mm Hg or less—then peripheral chemoreceptors stimulate an increase in respiratory activity. The chemoreceptors are only able to sense dissolved oxygen molecules, not the oxygen that is bound to hemoglobin. As you recall, the majority of oxygen is bound by hemoglobin; when dissolved levels of oxygen drop, hemoglobin releases oxygen. Therefore, a large drop in oxygen levels is required to stimulate the chemoreceptors of the aortic arch and carotid arteries.

The hypothalamus and other brain regions associated with the limbic system also play roles in influencing the regulation of breathing by interacting with the respiratory centers. The hypothalamus and other regions associated with the limbic system are involved in regulating respiration in response to emotions, pain, and temperature. For example, an increase in body temperature causes an increase in respiratory rate. Feeling excited or the fight-or-flight response will also result in an increase in respiratory rate.

# Disorders OF THE...

## Respiratory System: Sleep Apnea

Sleep apnea is a chronic disorder that can occur in children or adults, and is characterized by the cessation of breathing during sleep. These episodes may last for several seconds or several minutes, and may differ in the frequency with which they are experienced. Sleep apnea leads to poor sleep, which is reflected in the symptoms of fatigue, evening napping, irritability, memory problems, and morning headaches. In addition, many individuals with sleep apnea experience a dry throat in the morning after waking from sleep, which may be due to excessive snoring.

There are two types of sleep apnea: obstructive sleep apnea and central sleep apnea. Obstructive sleep apnea is caused by an obstruction of the airway during sleep, which can occur at different points in the airway, depending on the underlying cause of the obstruction. For example, the tongue and throat muscles of some individuals with obstructive sleep apnea may relax excessively, causing the muscles to push into the airway. Another example is obesity, which is a known risk factor for sleep apnea, as excess adipose tissue in the neck region can push the soft tissues towards the lumen of the airway, causing the trachea to narrow.

In central sleep apnea, the respiratory centers of the brain do not respond properly to rising carbon dioxide levels and therefore do not stimulate the contraction of the diaphragm and intercostal muscles regularly. As a result, inspiration does not occur and breathing stops for a short period. In some cases, the cause of central sleep apnea is unknown. However, some medical conditions, such as stroke and congestive heart failure, may cause damage to the pons or medulla oblongata. In addition, some pharmacologic agents, such as morphine, can affect the respiratory centers, causing a decrease in the respiratory rate. The symptoms of central sleep apnea are similar to those of obstructive sleep apnea.

A diagnosis of sleep apnea is usually done during a sleep study, where the patient is monitored in a sleep laboratory for several nights. The patient's blood oxygen levels, heart rate, respiratory rate, and blood pressure are monitored, as are brain activity and the volume of air that is inhaled and exhaled. Treatment of sleep apnea commonly includes the use of a device called a continuous positive airway pressure (CPAP) machine during sleep. The CPAP machine has a mask that covers the nose, or the nose and mouth, and forces air into the airway at regular intervals. This pressurized air can help to gently force the airway to remain open, allowing more normal ventilation to occur. Other treatments include lifestyle changes to decrease weight, eliminate alcohol and other sleep apnea-promoting drugs, and changes in sleep position. In addition to these treatments, patients with central sleep apnea may need supplemental oxygen during sleep.

## 22.4 | Gas Exchange

By the end of this section, you will be able to:

- Compare the composition of atmospheric air and alveolar air
- Describe the mechanisms that drive gas exchange
- Discuss the importance of sufficient ventilation and perfusion, and how the body adapts when they are insufficient
- Discuss the process of external respiration
- Describe the process of internal respiration

The purpose of the respiratory system is to perform gas exchange. Pulmonary ventilation provides air to the alveoli for this gas exchange process. At the respiratory membrane, where the alveolar and capillary walls meet, gases move across the membranes, with oxygen entering the bloodstream and carbon dioxide exiting. It is through this mechanism that blood is oxygenated and carbon dioxide, the waste product of cellular respiration, is removed from the body.

### Gas Exchange

In order to understand the mechanisms of gas exchange in the lung, it is important to understand the underlying principles of gases and their behavior. In addition to Boyle's law, several other gas laws help to describe the behavior of gases.

## Gas Laws and Air Composition

Gas molecules exert force on the surfaces with which they are in contact; this force is called pressure. In natural systems, gases are normally present as a mixture of different types of molecules. For example, the atmosphere consists of oxygen, nitrogen, carbon dioxide, and other gaseous molecules, and this gaseous mixture exerts a certain pressure referred to as atmospheric pressure (Table 22.2). **Partial pressure** ( $P_x$ ) is the pressure of a single type of gas in a mixture of gases. For example, in the atmosphere, oxygen exerts a partial pressure, and nitrogen exerts another partial pressure, independent of the partial pressure of oxygen (Figure 22.21). **Total pressure** is the sum of all the partial pressures of a gaseous mixture. **Dalton's law** describes the behavior of nonreactive gases in a gaseous mixture and states that a specific gas type in a mixture exerts its own pressure; thus, the total pressure exerted by a mixture of gases is the sum of the partial pressures of the gases in the mixture.

### Partial Pressures of Atmospheric Gases

Gas	Percent of total composition	Partial pressure (mm Hg)
Nitrogen (N <sub>2</sub> )	78.6	597.4
Oxygen (O <sub>2</sub> )	20.9	158.8
Water (H <sub>2</sub> O)	0.4	3.0
Carbon dioxide (CO <sub>2</sub> )	0.04	0.3
Others	0.06	0.5
Total composition/total atmospheric pressure	100%	760.0

Table 22.2



Figure 22.21 **Partial and Total Pressures of a Gas** Partial pressure is the force exerted by a gas. The sum of the partial pressures of all the gases in a mixture equals the total pressure.

Partial pressure is extremely important in predicting the movement of gases. Recall that gases tend to equalize their pressure in two regions that are connected. A gas will move from an area where its partial pressure is higher to an area where its partial pressure is lower. In addition, the greater the partial pressure difference between the two areas, the more rapid is the movement of gases.

### Solubility of Gases in Liquids

**Henry's law** describes the behavior of gases when they come into contact with a liquid, such as blood. Henry's law states that the concentration of gas in a liquid is directly proportional to the solubility and partial pressure of that gas. The greater the partial pressure of the gas, the greater the number of gas molecules that will dissolve in the liquid. The concentration of the gas in a liquid is also dependent on the solubility of the gas in the liquid. For example, although nitrogen is present in the atmosphere, very little nitrogen dissolves into the blood, because the solubility of nitrogen in blood is very low. The exception to this occurs in scuba divers; the composition of the compressed air that divers breathe causes nitrogen to have a higher partial pressure than normal, causing it to dissolve in the blood in greater amounts than normal. Too much nitrogen in the bloodstream results in a serious condition that can be fatal if not corrected. Gas molecules establish an equilibrium between those molecules dissolved in liquid and those in air.

The composition of air in the atmosphere and in the alveoli differs. In both cases, the relative concentration of gases is nitrogen > oxygen > water vapor > carbon dioxide. The amount of water vapor present in alveolar air is greater than that in atmospheric air (Table 22.3). Recall that the respiratory system works to humidify incoming air, thereby causing the air present in the alveoli to have a greater amount of water vapor than atmospheric air. In addition, alveolar air contains a greater amount of carbon dioxide and less oxygen than atmospheric air. This is no surprise, as gas exchange removes oxygen from and adds carbon dioxide to alveolar air. Both deep and forced breathing cause the alveolar air composition to be changed more rapidly than during quiet breathing. As a result, the partial pressures of oxygen and carbon dioxide change, affecting the diffusion process that moves these materials across the membrane. This will cause oxygen to enter and carbon dioxide to leave the blood more quickly.

### Composition and Partial Pressures of Alveolar Air

Gas	Percent of total composition	Partial pressure (mm Hg)
Nitrogen (N <sub>2</sub> )	74.9	569
Oxygen (O <sub>2</sub> )	13.7	104
Water (H <sub>2</sub> O)	6.2	40
Carbon dioxide (CO <sub>2</sub> )	5.2	47
Total composition/total alveolar pressure	100%	760.0

Table 22.3

### Ventilation and Perfusion

Two important aspects of gas exchange in the lung are ventilation and perfusion. **Ventilation** is the movement of air into and out of the lungs, and perfusion is the flow of blood in the pulmonary capillaries. For gas exchange to be efficient, the volumes involved in ventilation and perfusion should be compatible. However, factors such as regional gravity effects on blood, blocked alveolar ducts, or disease can cause ventilation and perfusion to be imbalanced.

The partial pressure of oxygen in alveolar air is about 104 mm Hg, whereas the partial pressure of oxygenated blood in pulmonary veins is about 100 mm Hg. When ventilation is sufficient, oxygen enters the alveoli at a high rate, and the partial pressure of oxygen in the alveoli remains high. In contrast, when ventilation is insufficient, the partial pressure of oxygen in the alveoli drops. Without the large difference in partial pressure between the alveoli and the blood, oxygen does not diffuse efficiently across the respiratory membrane. The body has mechanisms that counteract this problem. In cases when ventilation is not sufficient for an alveolus, the body redirects blood flow to alveoli that are receiving sufficient ventilation. This is achieved by constricting the pulmonary arterioles that serve the dysfunctional alveolus, which redirects blood to other alveoli that have sufficient ventilation. At the same time, the pulmonary arterioles that serve alveoli receiving sufficient ventilation vasodilate, which brings in greater blood flow. Factors such as carbon dioxide, oxygen, and pH levels can all serve as stimuli for adjusting blood flow in the capillary networks associated with the alveoli.

Ventilation is regulated by the diameter of the airways, whereas perfusion is regulated by the diameter of the blood vessels. The diameter of the bronchioles is sensitive to the partial pressure of carbon dioxide in the alveoli. A greater partial pressure of carbon dioxide in the alveoli causes the bronchioles to increase their diameter as will a decreased level of oxygen in the blood supply, allowing carbon dioxide to be exhaled from the body at a greater rate. As mentioned above, a greater partial pressure of oxygen in the alveoli causes the pulmonary arterioles to dilate, increasing blood flow.

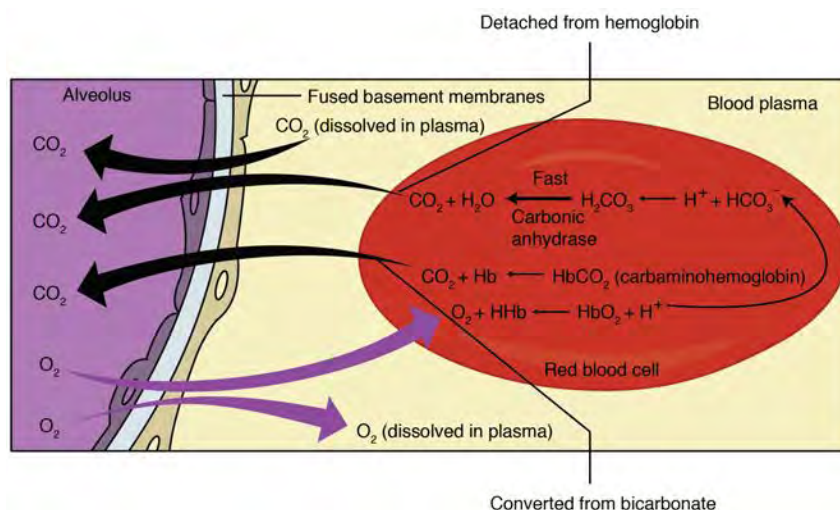
### Gas Exchange

Gas exchange occurs at two sites in the body: in the lungs, where oxygen is picked up and carbon dioxide is released at the respiratory membrane, and at the tissues, where oxygen is released and carbon dioxide is picked up. External respiration is the exchange of gases with the external environment, and occurs in the alveoli of the lungs. Internal respiration is the exchange of gases with the internal environment, and occurs in the tissues. The actual exchange of gases occurs due to simple diffusion. Energy is not required to move oxygen or carbon dioxide across membranes. Instead, these gases follow pressure gradients that allow them to diffuse. The anatomy of the lung maximizes the diffusion of gases: The respiratory membrane is highly permeable to gases; the respiratory and blood capillary membranes are very thin; and there is a large surface area throughout the lungs.

## External Respiration

The pulmonary artery carries deoxygenated blood into the lungs from the heart, where it branches and eventually becomes the capillary network composed of pulmonary capillaries. These pulmonary capillaries create the respiratory membrane with the alveoli (Figure 22.22). As the blood is pumped through this capillary network, gas exchange occurs. Although a small amount of the oxygen is able to dissolve directly into plasma from the alveoli, most of the oxygen is picked up by erythrocytes (red blood cells) and binds to a protein called hemoglobin, a process described later in this chapter. Oxygenated hemoglobin is red, causing the overall appearance of bright red oxygenated blood, which returns to the heart through the pulmonary veins. Carbon dioxide is released in the opposite direction of oxygen, from the blood to the alveoli. Some of the carbon dioxide is returned on hemoglobin, but can also be dissolved in plasma or is present as a converted form, also explained in greater detail later in this chapter.

**External respiration** occurs as a function of partial pressure differences in oxygen and carbon dioxide between the alveoli and the blood in the pulmonary capillaries.



**Figure 22.22 External Respiration** In external respiration, oxygen diffuses across the respiratory membrane from the alveolus to the capillary, whereas carbon dioxide diffuses out of the capillary into the alveolus.

Although the solubility of oxygen in blood is not high, there is a drastic difference in the partial pressure of oxygen in the alveoli versus in the blood of the pulmonary capillaries. This difference is about 64 mm Hg: The partial pressure of oxygen in the alveoli is about 104 mm Hg, whereas its partial pressure in the blood of the capillary is about 40 mm Hg. This large difference in partial pressure creates a very strong pressure gradient that causes oxygen to rapidly cross the respiratory membrane from the alveoli into the blood.

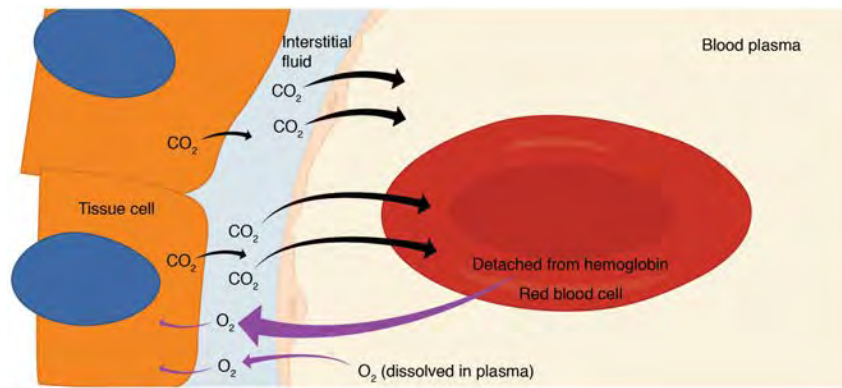
The partial pressure of carbon dioxide is also different between the alveolar air and the blood of the capillary. However, the partial pressure difference is less than that of oxygen, about 5 mm Hg. The partial pressure of carbon dioxide in the blood of the capillary is about 45 mm Hg, whereas its partial pressure in the alveoli is about 40 mm Hg. However, the solubility of carbon dioxide is much greater than that of oxygen—by a factor of about 20—in both blood and alveolar fluids. As a result, the relative concentrations of oxygen and carbon dioxide that diffuse across the respiratory membrane are similar.

## Internal Respiration

**Internal respiration** is gas exchange that occurs at the level of body tissues (Figure 22.23). Similar to external respiration, internal respiration also occurs as simple diffusion due to a partial pressure gradient. However, the partial pressure gradients are opposite of those present at the respiratory membrane. The partial pressure of oxygen in tissues is low, about 40 mm Hg, because oxygen is continuously used for cellular respiration. In contrast, the partial pressure of oxygen in the blood is about 100 mm Hg. This creates a pressure gradient that causes oxygen to dissociate from hemoglobin, diffuse out of the blood, cross the interstitial space, and enter the tissue. Hemoglobin that has little oxygen bound to it loses much of its brightness, so that blood returning to the heart is more burgundy in color.

Considering that cellular respiration continuously produces carbon dioxide, the partial pressure of carbon dioxide is lower in the blood than it is in the tissue, causing carbon dioxide to diffuse out of the tissue, cross the interstitial fluid, and enter the blood. It is then carried back to the lungs either bound to hemoglobin, dissolved in plasma, or in a converted form. By the time blood returns to the heart, the partial pressure of oxygen has returned to about 40 mm Hg, and the partial pressure

of carbon dioxide has returned to about 45 mm Hg. The blood is then pumped back to the lungs to be oxygenated once again during external respiration.



**Figure 22.23 Internal Respiration** Oxygen diffuses out of the capillary and into cells, whereas carbon dioxide diffuses out of cells and into the capillary.

## Everyday CONNECTION

### Hyperbaric Chamber Treatment

A type of device used in some areas of medicine that exploits the behavior of gases is hyperbaric chamber treatment. A hyperbaric chamber is a unit that can be sealed and expose a patient to either 100 percent oxygen with increased pressure or a mixture of gases that includes a higher concentration of oxygen than normal atmospheric air, also at a higher partial pressure than the atmosphere. There are two major types of chambers: monoplace and multiplace. Monoplace chambers are typically for one patient, and the staff tending to the patient observes the patient from outside of the chamber (**Figure 22.24**). Some facilities have special monoplace hyperbaric chambers that allow multiple patients to be treated at once, usually in a sitting or reclining position, to help ease feelings of isolation or claustrophobia. Multiplace chambers are large enough for multiple patients to be treated at one time, and the staff attending these patients is present inside the chamber. In a multiplace chamber, patients are often treated with air via a mask or hood, and the chamber is pressurized.



**Figure 22.24 Hyperbaric Chamber** (credit: "komunews"/flickr.com)

Hyperbaric chamber treatment is based on the behavior of gases. As you recall, gases move from a region of higher partial pressure to a region of lower partial pressure. In a hyperbaric chamber, the atmospheric pressure is increased, causing a greater amount of oxygen than normal to diffuse into the bloodstream of the patient. Hyperbaric chamber therapy is used to treat a variety of medical problems, such as wound and graft healing, anaerobic bacterial infections, and carbon monoxide poisoning. Exposure to and poisoning by carbon monoxide is difficult to reverse, because hemoglobin's affinity for carbon monoxide is much stronger than its affinity for oxygen, causing carbon monoxide to replace oxygen in the blood. Hyperbaric chamber therapy can treat carbon monoxide poisoning, because the increased atmospheric pressure causes more oxygen to diffuse into the bloodstream. At this increased pressure and increased concentration of oxygen, carbon monoxide is displaced from hemoglobin. Another example is the treatment of anaerobic bacterial infections, which are created by bacteria that cannot or prefer not to live in the presence of oxygen. An increase in blood and tissue levels of oxygen helps to kill the anaerobic bacteria that are responsible for the infection, as oxygen is toxic to anaerobic bacteria. For wounds and grafts, the chamber stimulates the healing process by increasing energy production needed for repair. Increasing oxygen transport allows cells to ramp up cellular respiration and thus ATP production, the energy needed to build new structures.

## 22.5 | Transport of Gases

By the end of this section, you will be able to:

- Describe the principles of oxygen transport
- Describe the structure of hemoglobin
- Compare and contrast fetal and adult hemoglobin
- Describe the principles of carbon dioxide transport

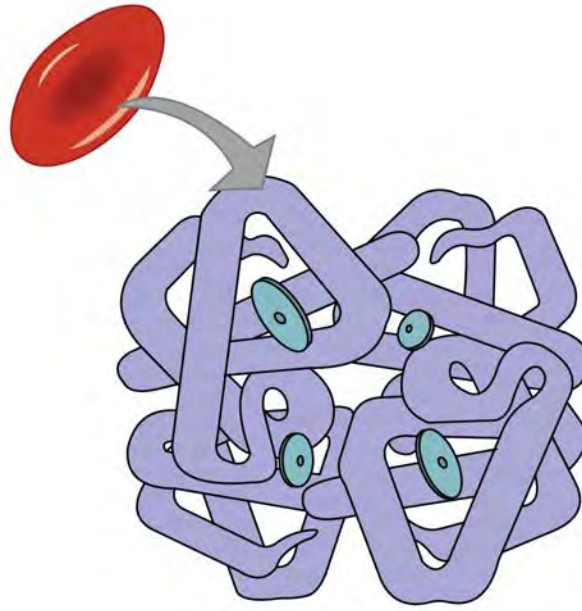
The other major activity in the lungs is the process of respiration, the process of gas exchange. The function of respiration is to provide oxygen for use by body cells during cellular respiration and to eliminate carbon dioxide, a waste product of cellular respiration, from the body. In order for the exchange of oxygen and carbon dioxide to occur, both gases must be transported between the external and internal respiration sites. Although carbon dioxide is more soluble than oxygen in blood, both gases require a specialized transport system for the majority of the gas molecules to be moved between the lungs and other tissues.

### Oxygen Transport in the Blood

Even though oxygen is transported via the blood, you may recall that oxygen is not very soluble in liquids. A small amount of oxygen does dissolve in the blood and is transported in the bloodstream, but it is only about 1.5% of the total amount. The majority of oxygen molecules are carried from the lungs to the body's tissues by a specialized transport system, which relies on the erythrocyte—the red blood cell. Erythrocytes contain a metalloprotein, hemoglobin, which serves to bind oxygen molecules to the erythrocyte (**Figure 22.25**). Heme is the portion of hemoglobin that contains iron, and it is heme that binds oxygen. One hemoglobin molecule contains iron-containing Heme molecules, and because of this, each hemoglobin molecule is capable of carrying up to four molecules of oxygen. As oxygen diffuses across the respiratory membrane from the alveolus to the capillary, it also diffuses into the red blood cell and is bound by hemoglobin. The following reversible chemical reaction describes the production of the final product, **oxyhemoglobin** (Hb-O<sub>2</sub>), which is formed when oxygen binds to hemoglobin. Oxyhemoglobin is a bright red-colored molecule that contributes to the bright red color of oxygenated blood.



In this formula, Hb represents reduced hemoglobin, that is, hemoglobin that does not have oxygen bound to it. There are multiple factors involved in how readily heme binds to and dissociates from oxygen, which will be discussed in the subsequent sections.



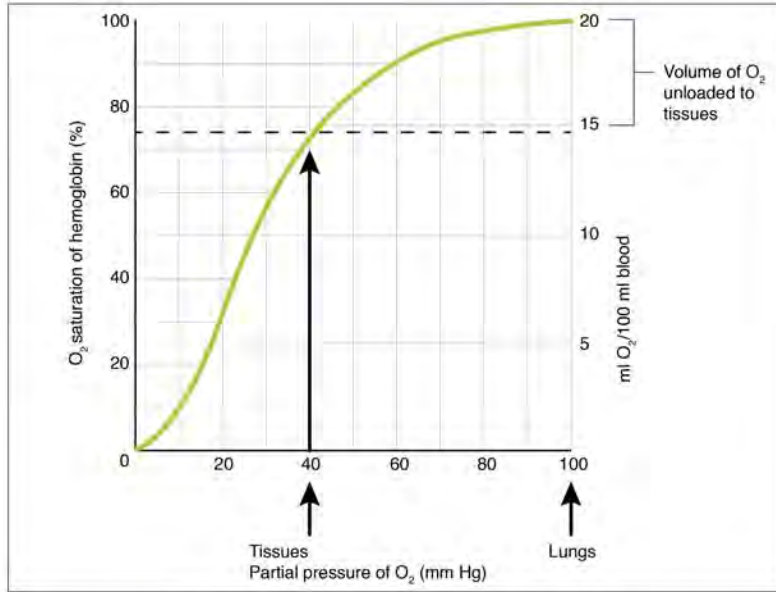
**Figure 22.25 Erythrocyte and Hemoglobin** Hemoglobin consists of four subunits, each of which contains one molecule of iron.

### Function of Hemoglobin

Hemoglobin is composed of subunits, a protein structure that is referred to as a quaternary structure. Each of the four subunits that make up hemoglobin is arranged in a ring-like fashion, with an iron atom covalently bound to the heme in the center of each subunit. Binding of the first oxygen molecule causes a conformational change in hemoglobin that allows the second molecule of oxygen to bind more readily. As each molecule of oxygen is bound, it further facilitates the binding of the next molecule, until all four heme sites are occupied by oxygen. The opposite occurs as well: After the first oxygen molecule dissociates and is “dropped off” at the tissues, the next oxygen molecule dissociates more readily. When all four heme sites are occupied, the hemoglobin is said to be saturated. When one to three heme sites are occupied, the hemoglobin is said to be partially saturated. Therefore, when considering the blood as a whole, the percent of the available heme units that are bound to oxygen at a given time is called hemoglobin saturation. Hemoglobin saturation of 100 percent means that every heme unit in all of the erythrocytes of the body is bound to oxygen. In a healthy individual with normal hemoglobin levels, hemoglobin saturation generally ranges from 95 percent to 99 percent.

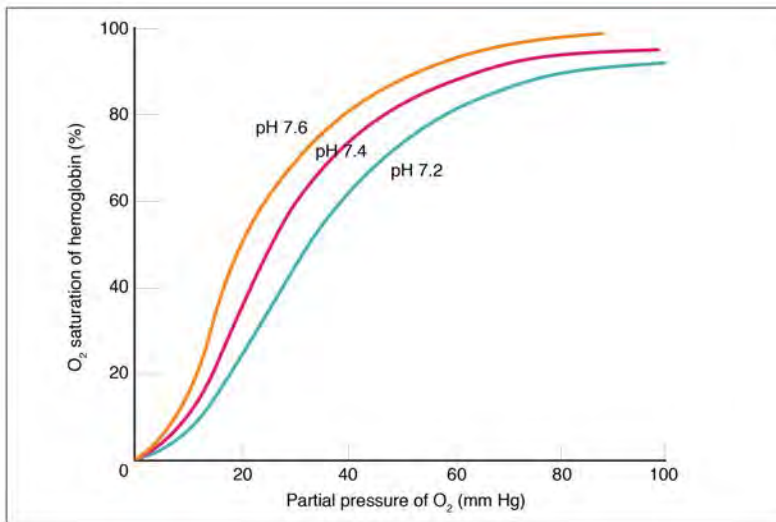
### Oxygen Dissociation from Hemoglobin

Partial pressure is an important aspect of the binding of oxygen to and disassociation from heme. An **oxygen–hemoglobin dissociation curve** is a graph that describes the relationship of partial pressure to the binding of oxygen to heme and its subsequent dissociation from heme (**Figure 22.26**). Remember that gases travel from an area of higher partial pressure to an area of lower partial pressure. In addition, the affinity of an oxygen molecule for heme increases as more oxygen molecules are bound. Therefore, in the oxygen–hemoglobin saturation curve, as the partial pressure of oxygen increases, a proportionately greater number of oxygen molecules are bound by heme. Not surprisingly, the oxygen–hemoglobin saturation/dissociation curve also shows that the lower the partial pressure of oxygen, the fewer oxygen molecules are bound to heme. As a result, the partial pressure of oxygen plays a major role in determining the degree of binding of oxygen to heme at the site of the respiratory membrane, as well as the degree of dissociation of oxygen from heme at the site of body tissues.



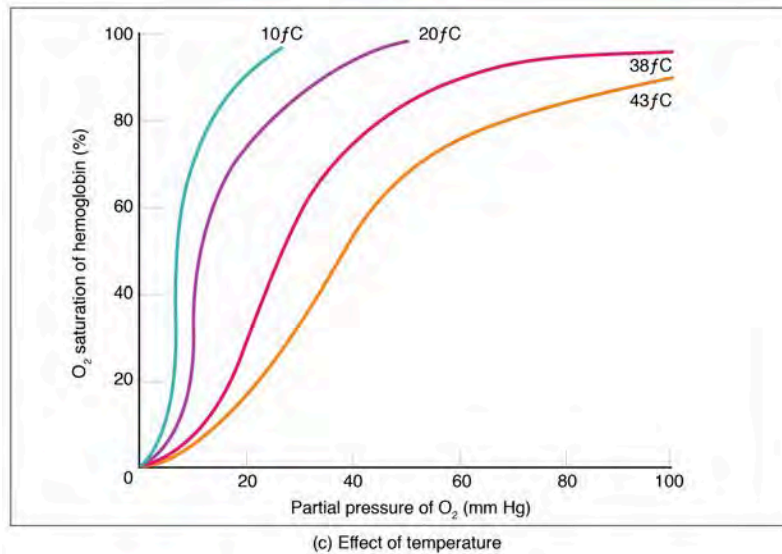
(a) Partial pressure of oxygen and hemoglobin saturation

(a)



(b) Effect of pH

(b)



(c)

**Figure 22.26 Oxygen-Hemoglobin Dissociation and Effects of pH and Temperature** These three graphs show (a) the relationship between the partial pressure of oxygen and hemoglobin saturation, (b) the effect of pH on the oxygen–hemoglobin dissociation curve, and (c) the effect of temperature on the oxygen–hemoglobin dissociation curve.

The mechanisms behind the oxygen–hemoglobin saturation/dissociation curve also serve as automatic control mechanisms that regulate how much oxygen is delivered to different tissues throughout the body. This is important because some tissues have a higher metabolic rate than others. Highly active tissues, such as muscle, rapidly use oxygen to produce ATP, lowering the partial pressure of oxygen in the tissue to about 20 mm Hg. The partial pressure of oxygen inside capillaries is about 100 mm Hg, so the difference between the two becomes quite high, about 80 mm Hg. As a result, a greater number of oxygen molecules dissociate from hemoglobin and enter the tissues. The reverse is true of tissues, such as adipose (body fat), which have lower metabolic rates. Because less oxygen is used by these cells, the partial pressure of oxygen within such tissues remains relatively high, resulting in fewer oxygen molecules dissociating from hemoglobin and entering the tissue interstitial fluid. Although venous blood is said to be deoxygenated, some oxygen is still bound to hemoglobin in its red blood cells. This provides an oxygen reserve that can be used when tissues suddenly demand more oxygen.

Factors other than partial pressure also affect the oxygen–hemoglobin saturation/dissociation curve. For example, a higher temperature promotes hemoglobin and oxygen to dissociate faster, whereas a lower temperature inhibits dissociation (see **Figure 22.26, middle**). However, the human body tightly regulates temperature, so this factor may not affect gas exchange throughout the body. The exception to this is in highly active tissues, which may release a larger amount of energy than is given off as heat. As a result, oxygen readily dissociates from hemoglobin, which is a mechanism that helps to provide active tissues with more oxygen.

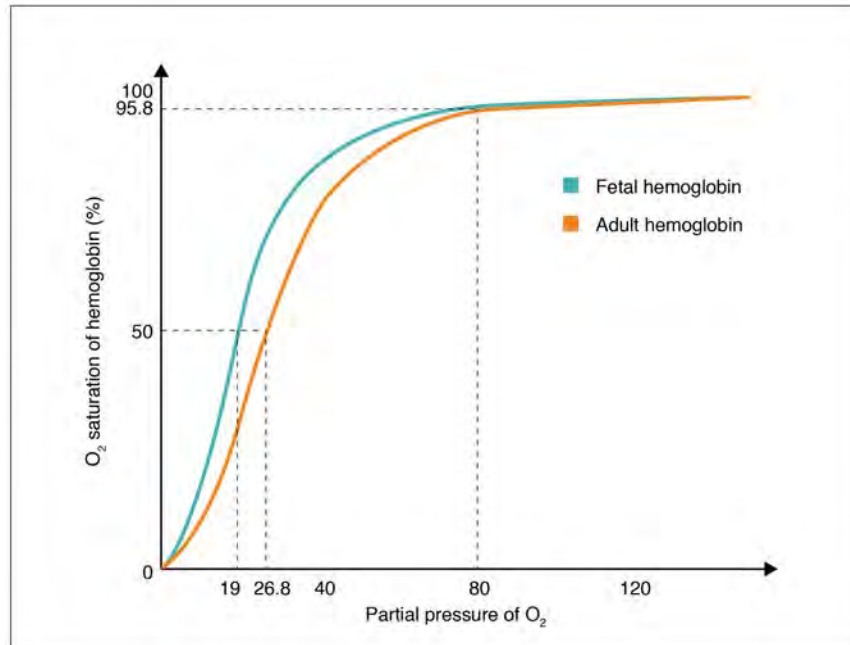
Certain hormones, such as androgens, epinephrine, thyroid hormones, and growth hormone, can affect the oxygen–hemoglobin saturation/dissociation curve by stimulating the production of a compound called 2,3-bisphosphoglycerate (BPG) by erythrocytes. BPG is a byproduct of glycolysis. Because erythrocytes do not contain mitochondria, glycolysis is the sole method by which these cells produce ATP. BPG promotes the disassociation of oxygen from hemoglobin. Therefore, the greater the concentration of BPG, the more readily oxygen dissociates from hemoglobin, despite its partial pressure.

The pH of the blood is another factor that influences the oxygen–hemoglobin saturation/dissociation curve (see **Figure 22.26**). The **Bohr effect** is a phenomenon that arises from the relationship between pH and oxygen’s affinity for hemoglobin: A lower, more acidic pH promotes oxygen dissociation from hemoglobin. In contrast, a higher, or more basic, pH inhibits oxygen dissociation from hemoglobin. The greater the amount of carbon dioxide in the blood, the more molecules that must be converted, which in turn generates hydrogen ions and thus lowers blood pH. Furthermore, blood pH may become more acidic when certain byproducts of cell metabolism, such as lactic acid, carbonic acid, and carbon dioxide, are released into the bloodstream.

### Hemoglobin of the Fetus

The fetus has its own circulation with its own erythrocytes; however, it is dependent on the mother for oxygen. Blood is

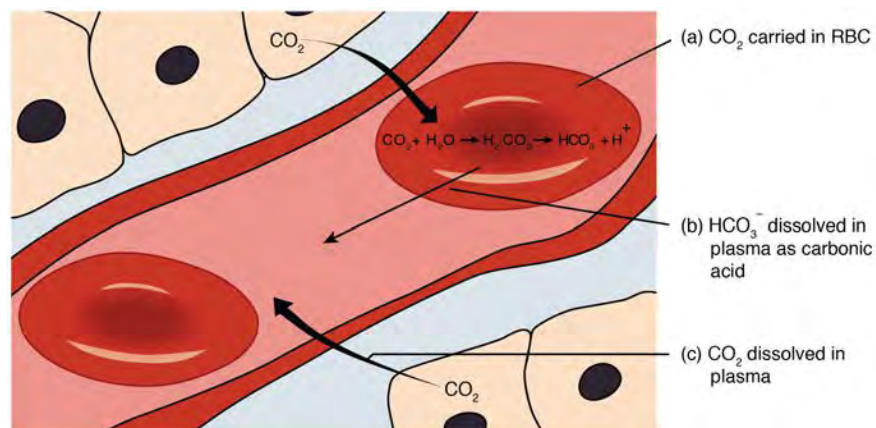
supplied to the fetus by way of the umbilical cord, which is connected to the placenta and separated from maternal blood by the chorion. The mechanism of gas exchange at the chorion is similar to gas exchange at the respiratory membrane. However, the partial pressure of oxygen is lower in the maternal blood in the placenta, at about 35 to 50 mm Hg, than it is in maternal arterial blood. The difference in partial pressures between maternal and fetal blood is not large, as the partial pressure of oxygen in fetal blood at the placenta is about 20 mm Hg. Therefore, there is not as much diffusion of oxygen into the fetal blood supply. The fetus' hemoglobin overcomes this problem by having a greater affinity for oxygen than maternal hemoglobin (**Figure 22.27**). Both fetal and adult hemoglobin have four subunits, but two of the subunits of fetal hemoglobin have a different structure that causes fetal hemoglobin to have a greater affinity for oxygen than does adult hemoglobin.



**Figure 22.27 Oxygen-Hemoglobin Dissociation Curves in Fetus and Adult** Fetal hemoglobin has a greater affinity for oxygen than does adult hemoglobin.

## Carbon Dioxide Transport in the Blood

Carbon dioxide is transported by three major mechanisms. The first mechanism of carbon dioxide transport is by blood plasma, as some carbon dioxide molecules dissolve in the blood. The second mechanism is transport in the form of bicarbonate ( $\text{HCO}_3^-$ ), which also dissolves in plasma. The third mechanism of carbon dioxide transport is similar to the transport of oxygen by erythrocytes (**Figure 22.28**).



**Figure 22.28 Carbon Dioxide Transport** Carbon dioxide is transported by three different methods: (a) in erythrocytes; (b) after forming carbonic acid ( $\text{H}_2\text{CO}_3$ ), which is dissolved in plasma; (c) and in plasma.

### Dissolved Carbon Dioxide

Although carbon dioxide is not considered to be highly soluble in blood, a small fraction—about 7 to 10 percent—of the carbon dioxide that diffuses into the blood from the tissues dissolves in plasma. The dissolved carbon dioxide then travels in the bloodstream and when the blood reaches the pulmonary capillaries, the dissolved carbon dioxide diffuses across the respiratory membrane into the alveoli, where it is then exhaled during pulmonary ventilation.

### Bicarbonate Buffer

A large fraction—about 70 percent—of the carbon dioxide molecules that diffuse into the blood is transported to the lungs as bicarbonate. Most bicarbonate is produced in erythrocytes after carbon dioxide diffuses into the capillaries, and subsequently into red blood cells. **Carbonic anhydrase (CA)** causes carbon dioxide and water to form carbonic acid ( $\text{H}_2\text{CO}_3$ ), which dissociates into two ions: bicarbonate ( $\text{HCO}_3^-$ ) and hydrogen ( $\text{H}^+$ ). The following formula depicts this reaction:

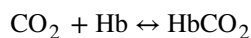


Bicarbonate tends to build up in the erythrocytes, so that there is a greater concentration of bicarbonate in the erythrocytes than in the surrounding blood plasma. As a result, some of the bicarbonate will leave the erythrocytes and move down its concentration gradient into the plasma in exchange for chloride ( $\text{Cl}^-$ ) ions. This phenomenon is referred to as the **chloride shift** and occurs because by exchanging one negative ion for another negative ion, neither the electrical charge of the erythrocytes nor that of the blood is altered.

At the pulmonary capillaries, the chemical reaction that produced bicarbonate (shown above) is reversed, and carbon dioxide and water are the products. Much of the bicarbonate in the plasma re-enters the erythrocytes in exchange for chloride ions. Hydrogen ions and bicarbonate ions join to form carbonic acid, which is converted into carbon dioxide and water by carbonic anhydrase. Carbon dioxide diffuses out of the erythrocytes and into the plasma, where it can further diffuse across the respiratory membrane into the alveoli to be exhaled during pulmonary ventilation.

### Carbaminohemoglobin

About 20 percent of carbon dioxide is bound by hemoglobin and is transported to the lungs. Carbon dioxide does not bind to iron as oxygen does; instead, carbon dioxide binds amino acid moieties on the globin portions of hemoglobin to form **carbaminohemoglobin**, which forms when hemoglobin and carbon dioxide bind. When hemoglobin is not transporting oxygen, it tends to have a bluish-purple tone to it, creating the darker maroon color typical of deoxygenated blood. The following formula depicts this reversible reaction:



Similar to the transport of oxygen by heme, the binding and dissociation of carbon dioxide to and from hemoglobin is dependent on the partial pressure of carbon dioxide. Because carbon dioxide is released from the lungs, blood that leaves the lungs and reaches body tissues has a lower partial pressure of carbon dioxide than is found in the tissues. As a result, carbon dioxide leaves the tissues because of its higher partial pressure, enters the blood, and then moves into red blood cells, binding to hemoglobin. In contrast, in the pulmonary capillaries, the partial pressure of carbon dioxide is high compared

to within the alveoli. As a result, carbon dioxide dissociates readily from hemoglobin and diffuses across the respiratory membrane into the air.

In addition to the partial pressure of carbon dioxide, the oxygen saturation of hemoglobin and the partial pressure of oxygen in the blood also influence the affinity of hemoglobin for carbon dioxide. The **Haldane effect** is a phenomenon that arises from the relationship between the partial pressure of oxygen and the affinity of hemoglobin for carbon dioxide. Hemoglobin that is saturated with oxygen does not readily bind carbon dioxide. However, when oxygen is not bound to heme and the partial pressure of oxygen is low, hemoglobin readily binds to carbon dioxide.

## Interactive LINK



Watch this **video** (<http://openstaxcollege.org/l/oxyblood>) to see the transport of oxygen from the lungs to the tissues. Why is oxygenated blood bright red, whereas deoxygenated blood tends to be more of a purple color?

## 22.6 | Modifications in Respiratory Functions

By the end of this section, you will be able to:

- Define the terms hyperpnea and hyperventilation
- Describe the effect of exercise on the respiratory system
- Describe the effect of high altitude on the respiratory system
- Discuss the process of acclimatization

At rest, the respiratory system performs its functions at a constant, rhythmic pace, as regulated by the respiratory centers of the brain. At this pace, ventilation provides sufficient oxygen to all the tissues of the body. However, there are times that the respiratory system must alter the pace of its functions in order to accommodate the oxygen demands of the body.

### Hyperpnea

**Hyperpnea** is an increased depth and rate of ventilation to meet an increase in oxygen demand as might be seen in exercise or disease, particularly diseases that target the respiratory or digestive tracts. This does not significantly alter blood oxygen or carbon dioxide levels, but merely increases the depth and rate of ventilation to meet the demand of the cells. In contrast, **hyperventilation** is an increased ventilation rate that is independent of the cellular oxygen needs and leads to abnormally low blood carbon dioxide levels and high (alkaline) blood pH.

Interestingly, exercise does not cause hyperpnea as one might think. Muscles that perform work during exercise do increase their demand for oxygen, stimulating an increase in ventilation. However, hyperpnea during exercise appears to occur before a drop in oxygen levels within the muscles can occur. Therefore, hyperpnea must be driven by other mechanisms, either instead of or in addition to a drop in oxygen levels. The exact mechanisms behind exercise hyperpnea are not well understood, and some hypotheses are somewhat controversial. However, in addition to low oxygen, high carbon dioxide, and low pH levels, there appears to be a complex interplay of factors related to the nervous system and the respiratory centers of the brain.

First, a conscious decision to partake in exercise, or another form of physical exertion, results in a psychological stimulus that may trigger the respiratory centers of the brain to increase ventilation. In addition, the respiratory centers of the brain may be stimulated through the activation of motor neurons that innervate muscle groups that are involved in the physical activity. Finally, physical exertion stimulates proprioceptors, which are receptors located within the muscles, joints, and

tendons, which sense movement and stretching; proprioceptors thus create a stimulus that may also trigger the respiratory centers of the brain. These neural factors are consistent with the sudden increase in ventilation that is observed immediately as exercise begins. Because the respiratory centers are stimulated by psychological, motor neuron, and proprioceptor inputs throughout exercise, the fact that there is also a sudden decrease in ventilation immediately after the exercise ends when these neural stimuli cease, further supports the idea that they are involved in triggering the changes of ventilation.

## High Altitude Effects

An increase in altitude results in a decrease in atmospheric pressure. Although the proportion of oxygen relative to gases in the atmosphere remains at 21 percent, its partial pressure decreases (**Table 22.4**). As a result, it is more difficult for a body to achieve the same level of oxygen saturation at high altitude than at low altitude, due to lower atmospheric pressure. In fact, hemoglobin saturation is lower at high altitudes compared to hemoglobin saturation at sea level. For example, hemoglobin saturation is about 67 percent at 19,000 feet above sea level, whereas it reaches about 98 percent at sea level.

**Partial Pressure of Oxygen at Different Altitudes**

Example location	Altitude (feet above sea level)	Atmospheric pressure (mm Hg)	Partial pressure of oxygen (mm Hg)
New York City, New York	0	760	159
Boulder, Colorado	5000	632	133
Aspen, Colorado	8000	565	118
Pike's Peak, Colorado	14,000	447	94
Denali (Mt. McKinley), Alaska	20,000	350	73
Mt. Everest, Tibet	29,000	260	54

**Table 22.4**

As you recall, partial pressure is extremely important in determining how much gas can cross the respiratory membrane and enter the blood of the pulmonary capillaries. A lower partial pressure of oxygen means that there is a smaller difference in partial pressures between the alveoli and the blood, so less oxygen crosses the respiratory membrane. As a result, fewer oxygen molecules are bound by hemoglobin. Despite this, the tissues of the body still receive a sufficient amount of oxygen during rest at high altitudes. This is due to two major mechanisms. First, the number of oxygen molecules that enter the tissue from the blood is nearly equal between sea level and high altitudes. At sea level, hemoglobin saturation is higher, but only a quarter of the oxygen molecules are actually released into the tissue. At high altitudes, a greater proportion of molecules of oxygen are released into the tissues. Secondly, at high altitudes, a greater amount of BPG is produced by erythrocytes, which enhances the dissociation of oxygen from hemoglobin. Physical exertion, such as skiing or hiking, can lead to altitude sickness due to the low amount of oxygen reserves in the blood at high altitudes. At sea level, there is a large amount of oxygen reserve in venous blood (even though venous blood is thought of as “deoxygenated”) from which the muscles can draw during physical exertion. Because the oxygen saturation is much lower at higher altitudes, this venous reserve is small, resulting in pathological symptoms of low blood oxygen levels. You may have heard that it is important to drink more water when traveling at higher altitudes than you are accustomed to. This is because your body will increase micturition (urination) at high altitudes to counteract the effects of lower oxygen levels. By removing fluids, blood plasma levels drop but not the total number of erythrocytes. In this way, the overall concentration of erythrocytes in the blood increases, which helps tissues obtain the oxygen they need.

**Acute mountain sickness (AMS)**, or altitude sickness, is a condition that results from acute exposure to high altitudes due to a low partial pressure of oxygen at high altitudes. AMS typically can occur at 2400 meters (8000 feet) above sea level. AMS is a result of low blood oxygen levels, as the body has acute difficulty adjusting to the low partial pressure of oxygen. In serious cases, AMS can cause pulmonary or cerebral edema. Symptoms of AMS include nausea, vomiting, fatigue, lightheadedness, drowsiness, feeling disoriented, increased pulse, and nosebleeds. The only treatment for AMS is descending to a lower altitude; however, pharmacologic treatments and supplemental oxygen can improve symptoms. AMS can be prevented by slowly ascending to the desired altitude, allowing the body to acclimate, as well as maintaining proper hydration.

## Acclimatization

Especially in situations where the ascent occurs too quickly, traveling to areas of high altitude can cause AMS. **Acclimatization** is the process of adjustment that the respiratory system makes due to chronic exposure to a high altitude. Over a period of time, the body adjusts to accommodate the lower partial pressure of oxygen. The low partial pressure of oxygen at high altitudes results in a lower oxygen saturation level of hemoglobin in the blood. In turn, the tissue levels of oxygen are also lower. As a result, the kidneys are stimulated to produce the hormone erythropoietin (EPO), which stimulates the production of erythrocytes, resulting in a greater number of circulating erythrocytes in an individual at a high altitude over a long period. With more red blood cells, there is more hemoglobin to help transport the available oxygen. Even though there is low saturation of each hemoglobin molecule, there will be more hemoglobin present, and therefore more oxygen in the blood. Over time, this allows the person to partake in physical exertion without developing AMS.

## 22.7 | Embryonic Development of the Respiratory System

By the end of this section, you will be able to:

- Create a timeline of the phases of respiratory development in the fetus
- Propose reasons for fetal breathing movements
- Explain how the lungs become inflated after birth

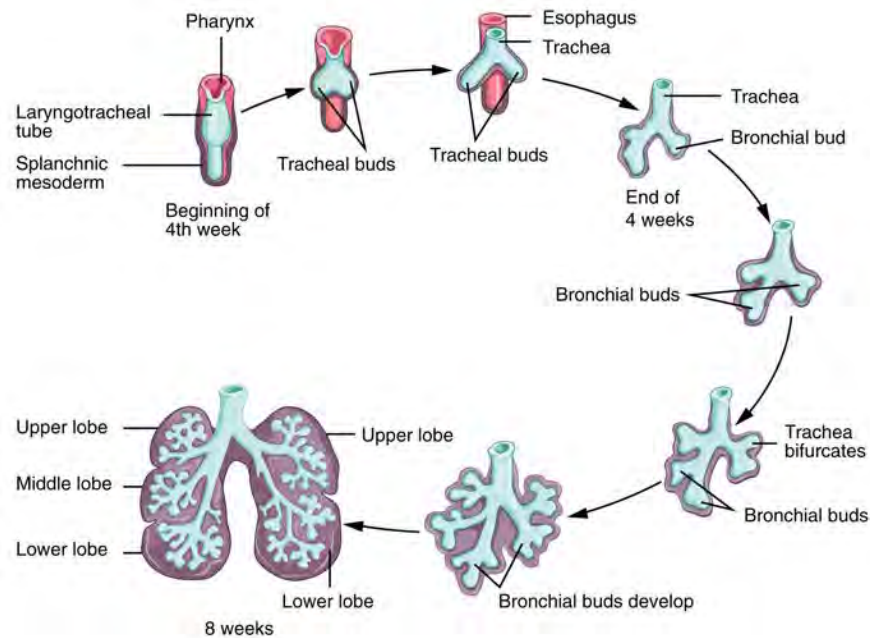
Development of the respiratory system begins early in the fetus. It is a complex process that includes many structures, most of which arise from the endoderm. Towards the end of development, the fetus can be observed making breathing movements. Until birth, however, the mother provides all of the oxygen to the fetus as well as removes all of the fetal carbon dioxide via the placenta.

### Time Line

The development of the respiratory system begins at about week 4 of gestation. By week 28, enough alveoli have matured that a baby born prematurely at this time can usually breathe on its own. The respiratory system, however, is not fully developed until early childhood, when a full complement of mature alveoli is present.

#### Weeks 4–7

Respiratory development in the embryo begins around week 4. Ectodermal tissue from the anterior head region invaginates posteriorly to form olfactory pits, which fuse with endodermal tissue of the developing pharynx. An **olfactory pit** is one of a pair of structures that will enlarge to become the nasal cavity. At about this same time, the lung bud forms. The **lung bud** is a dome-shaped structure composed of tissue that bulges from the foregut. The **foregut** is endoderm just inferior to the pharyngeal pouches. The **laryngotracheal bud** is a structure that forms from the longitudinal extension of the lung bud as development progresses. The portion of this structure nearest the pharynx becomes the trachea, whereas the distal end becomes more bulbous, forming bronchial buds. A **bronchial bud** is one of a pair of structures that will eventually become the bronchi and all other lower respiratory structures (**Figure 22.29**).



**Figure 22.29 Development of the Lower Respiratory System**

### Weeks 7–16

Bronchial buds continue to branch as development progresses until all of the segmental bronchi have been formed. Beginning around week 13, the lumens of the bronchi begin to expand in diameter. By week 16, respiratory bronchioles form. The fetus now has all major lung structures involved in the airway.

### Weeks 16–24

Once the respiratory bronchioles form, further development includes extensive vascularization, or the development of the blood vessels, as well as the formation of alveolar ducts and alveolar precursors. At about week 19, the respiratory bronchioles have formed. In addition, cells lining the respiratory structures begin to differentiate to form type I and type II pneumocytes. Once type II cells have differentiated, they begin to secrete small amounts of pulmonary surfactant. Around week 20, fetal breathing movements may begin.

### Weeks 24–Term

Major growth and maturation of the respiratory system occurs from week 24 until term. More alveolar precursors develop, and larger amounts of pulmonary surfactant are produced. Surfactant levels are not generally adequate to create effective lung compliance until about the eighth month of pregnancy. The respiratory system continues to expand, and the surfaces that will form the respiratory membrane develop further. At this point, pulmonary capillaries have formed and continue to expand, creating a large surface area for gas exchange. The major milestone of respiratory development occurs at around week 28, when sufficient alveolar precursors have matured so that a baby born prematurely at this time can usually breathe on its own. However, alveoli continue to develop and mature into childhood. A full complement of functional alveoli does not appear until around 8 years of age.

## Fetal “Breathing”

Although the function of fetal breathing movements is not entirely clear, they can be observed starting at 20–21 weeks of development. Fetal breathing movements involve muscle contractions that cause the inhalation of amniotic fluid and exhalation of the same fluid, with pulmonary surfactant and mucus. Fetal breathing movements are not continuous and may include periods of frequent movements and periods of no movements. Maternal factors can influence the frequency of breathing movements. For example, high blood glucose levels, called hyperglycemia, can boost the number of breathing movements. Conversely, low blood glucose levels, called hypoglycemia, can reduce the number of fetal breathing movements. Tobacco use is also known to lower fetal breathing rates. Fetal breathing may help tone the muscles in preparation for breathing movements once the fetus is born. It may also help the alveoli to form and mature. Fetal breathing movements are considered a sign of robust health.

## Birth

Prior to birth, the lungs are filled with amniotic fluid, mucus, and surfactant. As the fetus is squeezed through the birth canal, the fetal thoracic cavity is compressed, expelling much of this fluid. Some fluid remains, however, but is rapidly absorbed by the body shortly after birth. The first inhalation occurs within 10 seconds after birth and not only serves as the first inspiration, but also acts to inflate the lungs. Pulmonary surfactant is critical for inflation to occur, as it reduces the surface tension of the alveoli. Preterm birth around 26 weeks frequently results in severe respiratory distress, although with current medical advancements, some babies may survive. Prior to 26 weeks, sufficient pulmonary surfactant is not produced, and the surfaces for gas exchange have not formed adequately; therefore, survival is low.

# Disorders OF THE...

## Respiratory System: Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) primarily occurs in infants born prematurely. Up to 50 percent of infants born between 26 and 28 weeks and fewer than 30 percent of infants born between 30 and 31 weeks develop RDS. RDS results from insufficient production of pulmonary surfactant, thereby preventing the lungs from properly inflating at birth. A small amount of pulmonary surfactant is produced beginning at around 20 weeks; however, this is not sufficient for inflation of the lungs. As a result, dyspnea occurs and gas exchange cannot be performed properly. Blood oxygen levels are low, whereas blood carbon dioxide levels and pH are high.

The primary cause of RDS is premature birth, which may be due to a variety of known or unknown causes. Other risk factors include gestational diabetes, cesarean delivery, second-born twins, and family history of RDS. The presence of RDS can lead to other serious disorders, such as septicemia (infection of the blood) or pulmonary hemorrhage. Therefore, it is important that RDS is immediately recognized and treated to prevent death and reduce the risk of developing other disorders.

Medical advances have resulted in an improved ability to treat RDS and support the infant until proper lung development can occur. At the time of delivery, treatment may include resuscitation and intubation if the infant does not breathe on his or her own. These infants would need to be placed on a ventilator to mechanically assist with the breathing process. If spontaneous breathing occurs, application of nasal continuous positive airway pressure (CPAP) may be required. In addition, pulmonary surfactant is typically administered. Death due to RDS has been reduced by 50 percent due to the introduction of pulmonary surfactant therapy. Other therapies may include corticosteroids, supplemental oxygen, and assisted ventilation. Supportive therapies, such as temperature regulation, nutritional support, and antibiotics, may be administered to the premature infant as well.

## KEY TERMS

**acclimatization** process of adjustment that the respiratory system makes due to chronic exposure to high altitudes

**acute mountain sickness (AMS)** condition that occurs a result of acute exposure to high altitude due to a low partial pressure of oxygen

**ala** (plural = alae) small, flaring structure of a nostril that forms the lateral side of the nares

**alar cartilage** cartilage that supports the apex of the nose and helps shape the nares; it is connected to the septal cartilage and connective tissue of the alae

**alveolar dead space** air space within alveoli that are unable to participate in gas exchange

**alveolar duct** small tube that leads from the terminal bronchiole to the respiratory bronchiole and is the point of attachment for alveoli

**alveolar macrophage** immune system cell of the alveolus that removes debris and pathogens

**alveolar pore** opening that allows airflow between neighboring alveoli

**alveolar sac** cluster of alveoli

**alveolus** small, grape-like sac that performs gas exchange in the lungs

**anatomical dead space** air space present in the airway that never reaches the alveoli and therefore never participates in gas exchange

**apex** tip of the external nose

**apneustic center** network of neurons within the pons that stimulate the neurons in the dorsal respiratory group; controls the depth of inspiration

**atmospheric pressure** amount of force that is exerted by gases in the air surrounding any given surface

**Bohr effect** relationship between blood pH and oxygen dissociation from hemoglobin

**Boyle's law** relationship between volume and pressure as described by the formula:  $P_1V_1 = P_2V_2$

**bridge** portion of the external nose that lies in the area of the nasal bones

**bronchial bud** structure in the developing embryo that forms when the laryngotracheal bud extends and branches to form two bulbous structures

**bronchial tree** collective name for the multiple branches of the bronchi and bronchioles of the respiratory system

**bronchiole** branch of bronchi that are 1 mm or less in diameter and terminate at alveolar sacs

**bronchoconstriction** decrease in the size of the bronchiole due to contraction of the muscular wall

**bronchodilation** increase in the size of the bronchiole due to contraction of the muscular wall

**bronchus** tube connected to the trachea that branches into many subsidiaries and provides a passageway for air to enter and leave the lungs

**carbaminohemoglobin** bound form of hemoglobin and carbon dioxide

**carbonic anhydrase (CA)** enzyme that catalyzes the reaction that causes carbon dioxide and water to form carbonic acid

**cardiac notch** indentation on the surface of the left lung that allows space for the heart

**central chemoreceptor** one of the specialized receptors that are located in the brain that sense changes in hydrogen

ion, oxygen, or carbon dioxide concentrations in the brain

**chloride shift** facilitated diffusion that exchanges bicarbonate ( $\text{HCO}_3^-$ ) with chloride ( $\text{Cl}^-$ ) ions

**conducting zone** region of the respiratory system that includes the organs and structures that provide passageways for air and are not directly involved in gas exchange

**cricoid cartilage** portion of the larynx composed of a ring of cartilage with a wide posterior region and a thinner anterior region; attached to the esophagus

**Dalton's law** statement of the principle that a specific gas type in a mixture exerts its own pressure, as if that specific gas type was not part of a mixture of gases

**dorsal respiratory group (DRG)** region of the medulla oblongata that stimulates the contraction of the diaphragm and intercostal muscles to induce inspiration

**dorsum nasi** intermediate portion of the external nose that connects the bridge to the apex and is supported by the nasal bone

**epiglottis** leaf-shaped piece of elastic cartilage that is a portion of the larynx that swings to close the trachea during swallowing

**expiration** (also, exhalation) process that causes the air to leave the lungs

**expiratory reserve volume (ERV)** amount of air that can be forcefully exhaled after a normal tidal exhalation

**external nose** region of the nose that is easily visible to others

**external respiration** gas exchange that occurs in the alveoli

**fauces** portion of the posterior oral cavity that connects the oral cavity to the oropharynx

**fibroelastic membrane** specialized membrane that connects the ends of the C-shape cartilage in the trachea; contains smooth muscle fibers

**forced breathing** (also, hyperpnea) mode of breathing that occurs during exercise or by active thought that requires muscle contraction for both inspiration and expiration

**foregut** endoderm of the embryo towards the head region

**functional residual capacity (FRC)** sum of ERV and RV, which is the amount of air that remains in the lungs after a tidal expiration

**glottis** opening between the vocal folds through which air passes when producing speech

**Haldane effect** relationship between the partial pressure of oxygen and the affinity of hemoglobin for carbon dioxide

**Henry's law** statement of the principle that the concentration of gas in a liquid is directly proportional to the solubility and partial pressure of that gas

**hilum** concave structure on the mediastinal surface of the lungs where blood vessels, lymphatic vessels, nerves, and a bronchus enter the lung

**hyperpnea** increased rate and depth of ventilation due to an increase in oxygen demand that does not significantly alter blood oxygen or carbon dioxide levels

**hyperventilation** increased ventilation rate that leads to abnormally low blood carbon dioxide levels and high (alkaline) blood pH

**inspiration** (also, inhalation) process that causes air to enter the lungs

**inspiratory capacity (IC)** sum of the TV and IRV, which is the amount of air that can maximally be inhaled past a tidal expiration

**inspiratory reserve volume (IRV)** amount of air that enters the lungs due to deep inhalation past the tidal volume

**internal respiration** gas exchange that occurs at the level of body tissues

**intra-alveolar pressure** (intrapulmonary pressure) pressure of the air within the alveoli

**intrapleural pressure** pressure of the air within the pleural cavity

**laryngeal prominence** region where the two lamina of the thyroid cartilage join, forming a protrusion known as “Adam’s apple”

**laryngopharynx** portion of the pharynx bordered by the oropharynx superiorly and esophagus and trachea inferiorly; serves as a route for both air and food

**laryngotracheal bud** forms from the lung bud, has a tracheal end and bulbous bronchial buds at the distal end

**larynx** cartilaginous structure that produces the voice, prevents food and beverages from entering the trachea, and regulates the volume of air that enters and leaves the lungs

**lingual tonsil** lymphoid tissue located at the base of the tongue

**lung** organ of the respiratory system that performs gas exchange

**lung bud** median dome that forms from the endoderm of the foregut

**meatus** one of three recesses (superior, middle, and inferior) in the nasal cavity attached to the conchae that increase the surface area of the nasal cavity

**naris** (plural = nares) opening of the nostrils

**nasal bone** bone of the skull that lies under the root and bridge of the nose and is connected to the frontal and maxillary bones

**nasal septum** wall composed of bone and cartilage that separates the left and right nasal cavities

**nasopharynx** portion of the pharynx flanked by the conchae and oropharynx that serves as an airway

**olfactory pit** invaginated ectodermal tissue in the anterior portion of the head region of an embryo that will form the nasal cavity

**oropharynx** portion of the pharynx flanked by the nasopharynx, oral cavity, and laryngopharynx that is a passageway for both air and food

**oxygen–hemoglobin dissociation curve** graph that describes the relationship of partial pressure to the binding and disassociation of oxygen to and from heme

**oxyhemoglobin** (Hb–O<sub>2</sub>) bound form of hemoglobin and oxygen

**palatine tonsil** one of the paired structures composed of lymphoid tissue located anterior to the uvula at the roof of isthmus of the fauces

**paranasal sinus** one of the cavities within the skull that is connected to the conchae that serve to warm and humidify incoming air, produce mucus, and lighten the weight of the skull; consists of frontal, maxillary, sphenoidal, and ethmoidal sinuses

**parietal pleura** outermost layer of the pleura that connects to the thoracic wall, mediastinum, and diaphragm

**partial pressure** force exerted by each gas in a mixture of gases

**peripheral chemoreceptor** one of the specialized receptors located in the aortic arch and carotid arteries that sense changes in pH, carbon dioxide, or oxygen blood levels

**pharyngeal tonsil** structure composed of lymphoid tissue located in the nasopharynx

**pharynx** region of the conducting zone that forms a tube of skeletal muscle lined with respiratory epithelium; located between the nasal conchae and the esophagus and trachea

**philtrum** concave surface of the face that connects the apex of the nose to the top lip

**pleural cavity** space between the visceral and parietal pleurae

**pleural fluid** substance that acts as a lubricant for the visceral and parietal layers of the pleura during the movement of breathing

**pneumotaxic center** network of neurons within the pons that inhibit the activity of the neurons in the dorsal respiratory group; controls rate of breathing

**pulmonary artery** artery that arises from the pulmonary trunk and carries deoxygenated, arterial blood to the alveoli

**pulmonary plexus** network of autonomic nervous system fibers found near the hilum of the lung

**pulmonary surfactant** substance composed of phospholipids and proteins that reduces the surface tension of the alveoli; made by type II alveolar cells

**pulmonary ventilation** exchange of gases between the lungs and the atmosphere; breathing

**quiet breathing** (also, eupnea) mode of breathing that occurs at rest and does not require the cognitive thought of the individual

**residual volume (RV)** amount of air that remains in the lungs after maximum exhalation

**respiratory bronchiole** specific type of bronchiole that leads to alveolar sacs

**respiratory cycle** one sequence of inspiration and expiration

**respiratory epithelium** ciliated lining of much of the conducting zone that is specialized to remove debris and pathogens, and produce mucus

**respiratory membrane** alveolar and capillary wall together, which form an air-blood barrier that facilitates the simple diffusion of gases

**respiratory rate** total number of breaths taken each minute

**respiratory volume** varying amounts of air within the lung at a given time

**respiratory zone** includes structures of the respiratory system that are directly involved in gas exchange

**root** region of the external nose between the eyebrows

**thoracic wall compliance** ability of the thoracic wall to stretch while under pressure

**thyroid cartilage** largest piece of cartilage that makes up the larynx and consists of two lamina

**tidal volume (TV)** amount of air that normally enters the lungs during quiet breathing

**total dead space** sum of the anatomical dead space and alveolar dead space

**total lung capacity (TLC)** total amount of air that can be held in the lungs; sum of TV, ERV, IRV, and RV

**total pressure** sum of all the partial pressures of a gaseous mixture

**trachea** tube composed of cartilaginous rings and supporting tissue that connects the lung bronchi and the larynx; provides a route for air to enter and exit the lung

**trachealis muscle** smooth muscle located in the fibroelastic membrane of the trachea

**transpulmonary pressure** pressure difference between the intrapleural and intra-alveolar pressures

**true vocal cord** one of the pair of folded, white membranes that have a free inner edge that oscillates as air passes through to produce sound

**type I alveolar cell** squamous epithelial cells that are the major cell type in the alveolar wall; highly permeable to gases

**type II alveolar cell** cuboidal epithelial cells that are the minor cell type in the alveolar wall; secrete pulmonary surfactant

**ventilation** movement of air into and out of the lungs; consists of inspiration and expiration

**ventral respiratory group (VRG)** region of the medulla oblongata that stimulates the contraction of the accessory muscles involved in respiration to induce forced inspiration and expiration

**vestibular fold** part of the folded region of the glottis composed of mucous membrane; supports the epiglottis during swallowing

**visceral pleura** innermost layer of the pleura that is superficial to the lungs and extends into the lung fissures

**vital capacity (VC)** sum of TV, ERV, and IRV, which is all the volumes that participate in gas exchange

## CHAPTER REVIEW

### 22.1 Organs and Structures of the Respiratory System

The respiratory system is responsible for obtaining oxygen and getting rid of carbon dioxide, and aiding in speech production and in sensing odors. From a functional perspective, the respiratory system can be divided into two major areas: the conducting zone and the respiratory zone. The conducting zone consists of all of the structures that provide passageways for air to travel into and out of the lungs: the nasal cavity, pharynx, trachea, bronchi, and most bronchioles. The nasal passages contain the conchae and meatuses that expand the surface area of the cavity, which helps to warm and humidify incoming air, while removing debris and pathogens. The pharynx is composed of three major sections: the nasopharynx, which is continuous with the nasal cavity; the oropharynx, which borders the nasopharynx and the oral cavity; and the laryngopharynx, which borders the oropharynx, trachea, and esophagus. The respiratory zone includes the structures of the lung that are directly involved in gas exchange: the terminal bronchioles and alveoli.

The lining of the conducting zone is composed mostly of pseudostratified ciliated columnar epithelium with goblet cells. The mucus traps pathogens and debris, whereas beating cilia move the mucus superiorly toward the throat, where it is swallowed. As the bronchioles become smaller and smaller, and nearer the alveoli, the epithelium thins and is simple squamous epithelium in the alveoli. The endothelium of the surrounding capillaries, together with the alveolar epithelium, forms the respiratory membrane. This is a blood-air barrier through which gas exchange occurs by simple diffusion.

### 22.2 The Lungs

The lungs are the major organs of the respiratory system and are responsible for performing gas exchange. The lungs are paired and separated into lobes; The left lung consists of two lobes, whereas the right lung consists of three lobes. Blood circulation is very important, as blood is required to transport oxygen from the lungs to other tissues throughout the body. The function of the pulmonary circulation is to aid in gas exchange. The pulmonary artery provides deoxygenated blood to the capillaries that form respiratory membranes with the alveoli, and the pulmonary veins return newly oxygenated blood to the heart for further transport throughout the body. The lungs are innervated by the parasympathetic and sympathetic nervous systems, which coordinate the bronchodilation and bronchoconstriction of the airways. The lungs are enclosed by the pleura, a membrane that is composed of visceral and parietal pleural layers. The space between these two layers is called the pleural cavity. The mesothelial cells of the pleural membrane create pleural fluid, which serves as both a lubricant (to reduce friction during breathing) and as an adhesive to adhere the lungs to the thoracic wall (to facilitate movement of the lungs during ventilation).

### 22.3 The Process of Breathing

Pulmonary ventilation is the process of breathing, which is driven by pressure differences between the lungs and the atmosphere. Atmospheric pressure is the force exerted by gases present in the atmosphere. The force exerted by gases within the alveoli is called intra-alveolar (intrapulmonary) pressure, whereas the force exerted by gases in the pleural cavity is called intrapleural pressure. Typically, intrapleural pressure is lower, or negative to, intra-alveolar pressure. The difference

in pressure between intrapleural and intra-alveolar pressures is called transpulmonary pressure. In addition, intra-alveolar pressure will equalize with the atmospheric pressure. Pressure is determined by the volume of the space occupied by a gas and is influenced by resistance. Air flows when a pressure gradient is created, from a space of higher pressure to a space of lower pressure. Boyle's law describes the relationship between volume and pressure. A gas is at lower pressure in a larger volume because the gas molecules have more space in which to move. The same quantity of gas in a smaller volume results in gas molecules crowding together, producing increased pressure.

Resistance is created by inelastic surfaces, as well as the diameter of the airways. Resistance reduces the flow of gases. The surface tension of the alveoli also influences pressure, as it opposes the expansion of the alveoli. However, pulmonary surfactant helps to reduce the surface tension so that the alveoli do not collapse during expiration. The ability of the lungs to stretch, called lung compliance, also plays a role in gas flow. The more the lungs can stretch, the greater the potential volume of the lungs. The greater the volume of the lungs, the lower the air pressure within the lungs.

Pulmonary ventilation consists of the process of inspiration (or inhalation), where air enters the lungs, and expiration (or exhalation), where air leaves the lungs. During inspiration, the diaphragm and external intercostal muscles contract, causing the rib cage to expand and move outward, and expanding the thoracic cavity and lung volume. This creates a lower pressure within the lung than that of the atmosphere, causing air to be drawn into the lungs. During expiration, the diaphragm and intercostals relax, causing the thorax and lungs to recoil. The air pressure within the lungs increases to above the pressure of the atmosphere, causing air to be forced out of the lungs. However, during forced exhalation, the internal intercostals and abdominal muscles may be involved in forcing air out of the lungs.

Respiratory volume describes the amount of air in a given space within the lungs, or which can be moved by the lung, and is dependent on a variety of factors. Tidal volume refers to the amount of air that enters the lungs during quiet breathing, whereas inspiratory reserve volume is the amount of air that enters the lungs when a person inhales past the tidal volume. Expiratory reserve volume is the extra amount of air that can leave with forceful expiration, following tidal expiration. Residual volume is the amount of air that is left in the lungs after expelling the expiratory reserve volume. Respiratory capacity is the combination of two or more volumes. Anatomical dead space refers to the air within the respiratory structures that never participates in gas exchange, because it does not reach functional alveoli. Respiratory rate is the number of breaths taken per minute, which may change during certain diseases or conditions.

Both respiratory rate and depth are controlled by the respiratory centers of the brain, which are stimulated by factors such as chemical and pH changes in the blood. These changes are sensed by central chemoreceptors, which are located in the brain, and peripheral chemoreceptors, which are located in the aortic arch and carotid arteries. A rise in carbon dioxide or a decline in oxygen levels in the blood stimulates an increase in respiratory rate and depth.

## 22.4 Gas Exchange

The behavior of gases can be explained by the principles of Dalton's law and Henry's law, both of which describe aspects of gas exchange. Dalton's law states that each specific gas in a mixture of gases exerts force (its partial pressure) independently of the other gases in the mixture. Henry's law states that the amount of a specific gas that dissolves in a liquid is a function of its partial pressure. The greater the partial pressure of a gas, the more of that gas will dissolve in a liquid, as the gas moves toward equilibrium. Gas molecules move down a pressure gradient; in other words, gas moves from a region of high pressure to a region of low pressure. The partial pressure of oxygen is high in the alveoli and low in the blood of the pulmonary capillaries. As a result, oxygen diffuses across the respiratory membrane from the alveoli into the blood. In contrast, the partial pressure of carbon dioxide is high in the pulmonary capillaries and low in the alveoli. Therefore, carbon dioxide diffuses across the respiratory membrane from the blood into the alveoli. The amount of oxygen and carbon dioxide that diffuses across the respiratory membrane is similar.

Ventilation is the process that moves air into and out of the alveoli, and perfusion affects the flow of blood in the capillaries. Both are important in gas exchange, as ventilation must be sufficient to create a high partial pressure of oxygen in the alveoli. If ventilation is insufficient and the partial pressure of oxygen drops in the alveolar air, the capillary is constricted and blood flow is redirected to alveoli with sufficient ventilation. External respiration refers to gas exchange that occurs in the alveoli, whereas internal respiration refers to gas exchange that occurs in the tissue. Both are driven by partial pressure differences.

## 22.5 Transport of Gases

Oxygen is primarily transported through the blood by erythrocytes. These cells contain a metalloprotein called hemoglobin, which is composed of four subunits with a ring-like structure. Each subunit contains one atom of iron bound to a molecule of heme. Heme binds oxygen so that each hemoglobin molecule can bind up to four oxygen molecules. When all of the heme units in the blood are bound to oxygen, hemoglobin is considered to be saturated. Hemoglobin is partially saturated when only some heme units are bound to oxygen. An oxygen-hemoglobin saturation/dissociation curve is a common way to

depict the relationship of how easily oxygen binds to or dissociates from hemoglobin as a function of the partial pressure of oxygen. As the partial pressure of oxygen increases, the more readily hemoglobin binds to oxygen. At the same time, once one molecule of oxygen is bound by hemoglobin, additional oxygen molecules more readily bind to hemoglobin. Other factors such as temperature, pH, the partial pressure of carbon dioxide, and the concentration of 2,3-bisphosphoglycerate can enhance or inhibit the binding of hemoglobin and oxygen as well. Fetal hemoglobin has a different structure than adult hemoglobin, which results in fetal hemoglobin having a greater affinity for oxygen than adult hemoglobin.

Carbon dioxide is transported in blood by three different mechanisms: as dissolved carbon dioxide, as bicarbonate, or as carbaminohemoglobin. A small portion of carbon dioxide remains. The largest amount of transported carbon dioxide is as bicarbonate, formed in erythrocytes. For this conversion, carbon dioxide is combined with water with the aid of an enzyme called carbonic anhydrase. This combination forms carbonic acid, which spontaneously dissociates into bicarbonate and hydrogen ions. As bicarbonate builds up in erythrocytes, it is moved across the membrane into the plasma in exchange for chloride ions by a mechanism called the chloride shift. At the pulmonary capillaries, bicarbonate re-enters erythrocytes in exchange for chloride ions, and the reaction with carbonic anhydrase is reversed, recreating carbon dioxide and water. Carbon dioxide then diffuses out of the erythrocyte and across the respiratory membrane into the air. An intermediate amount of carbon dioxide binds directly to hemoglobin to form carbaminohemoglobin. The partial pressures of carbon dioxide and oxygen, as well as the oxygen saturation of hemoglobin, influence how readily hemoglobin binds carbon dioxide. The less saturated hemoglobin is and the lower the partial pressure of oxygen in the blood is, the more readily hemoglobin binds to carbon dioxide. This is an example of the Haldane effect.

## 22.6 Modifications in Respiratory Functions

Normally, the respiratory centers of the brain maintain a consistent, rhythmic breathing cycle. However, in certain cases, the respiratory system must adjust to situational changes in order to supply the body with sufficient oxygen. For example, exercise results in increased ventilation, and chronic exposure to a high altitude results in a greater number of circulating erythrocytes. Hyperpnea, an increase in the rate and depth of ventilation, appears to be a function of three neural mechanisms that include a psychological stimulus, motor neuron activation of skeletal muscles, and the activation of proprioceptors in the muscles, joints, and tendons. As a result, hyperpnea related to exercise is initiated when exercise begins, as opposed to when tissue oxygen demand actually increases.

In contrast, acute exposure to a high altitude, particularly during times of physical exertion, does result in low blood and tissue levels of oxygen. This change is caused by a low partial pressure of oxygen in the air, because the atmospheric pressure at high altitudes is lower than the atmospheric pressure at sea level. This can lead to a condition called acute mountain sickness (AMS) with symptoms that include headaches, disorientation, fatigue, nausea, and lightheadedness. Over a long period of time, a person's body will adjust to the high altitude, a process called acclimatization. During acclimatization, the low tissue levels of oxygen will cause the kidneys to produce greater amounts of the hormone erythropoietin, which stimulates the production of erythrocytes. Increased levels of circulating erythrocytes provide an increased amount of hemoglobin that helps supply an individual with more oxygen, preventing the symptoms of AMS.

## 22.7 Embryonic Development of the Respiratory System

The development of the respiratory system in the fetus begins at about 4 weeks and continues into childhood. Ectodermal tissue in the anterior portion of the head region invaginates posteriorly, forming olfactory pits, which ultimately fuse with endodermal tissue of the early pharynx. At about this same time, an protrusion of endodermal tissue extends anteriorly from the foregut, producing a lung bud, which continues to elongate until it forms the laryngotracheal bud. The proximal portion of this structure will mature into the trachea, whereas the bulbous end will branch to form two bronchial buds. These buds then branch repeatedly, so that at about week 16, all major airway structures are present. Development progresses after week 16 as respiratory bronchioles and alveolar ducts form, and extensive vascularization occurs. Alveolar type I cells also begin to take shape. Type II pulmonary cells develop and begin to produce small amounts of surfactant. As the fetus grows, the respiratory system continues to expand as more alveoli develop and more surfactant is produced. Beginning at about week 36 and lasting into childhood, alveolar precursors mature to become fully functional alveoli. At birth, compression of the thoracic cavity forces much of the fluid in the lungs to be expelled. The first inhalation inflates the lungs. Fetal breathing movements begin around week 20 or 21, and occur when contractions of the respiratory muscles cause the fetus to inhale and exhale amniotic fluid. These movements continue until birth and may help to tone the muscles in preparation for breathing after birth and are a sign of good health.

## INTERACTIVE LINK QUESTIONS

1. Visit this [site \(http://openstaxcollege.org/l/asthma\)](http://openstaxcollege.org/l/asthma) to learn more about what happens during an asthma attack. What are the three changes that occur inside the airways during an asthma attack?
2. Watch this [video \(http://openstaxcollege.org/l/spirometers\)](http://openstaxcollege.org/l/spirometers) to learn more about lung volumes and spirometers. Explain how spirometry test results can be used to diagnose respiratory diseases or determine the effectiveness of disease treatment.
3. Watch this [video \(http://openstaxcollege.org/l/oxyblood\)](http://openstaxcollege.org/l/oxyblood) to see the transport of oxygen from the lungs to the tissues. Why is oxygenated blood bright red, whereas deoxygenated blood tends to be more of a purple color?

## REVIEW QUESTIONS

4. Which of the following anatomical structures is *not* part of the conducting zone?
  - a. pharynx
  - b. nasal cavity
  - c. alveoli
  - d. bronchi
5. What is the function of the conchae in the nasal cavity?
  - a. increase surface area
  - b. exchange gases
  - c. maintain surface tension
  - d. maintain air pressure
6. The fauces connects which of the following structures to the oropharynx?
  - a. nasopharynx
  - b. laryngopharynx
  - c. nasal cavity
  - d. oral cavity
7. Which of the following are structural features of the trachea?
  - a. C-shaped cartilage
  - b. smooth muscle fibers
  - c. cilia
  - d. all of the above
8. Which of the following structures is *not* part of the bronchial tree?
  - a. alveoli
  - b. bronchi
  - c. terminal bronchioles
  - d. respiratory bronchioles
9. What is the role of alveolar macrophages?
  - a. to secrete pulmonary surfactant
  - b. to secrete antimicrobial proteins
  - c. to remove pathogens and debris
  - d. to facilitate gas exchange
10. Which of the following structures separates the lung into lobes?
  - a. mediastinum
  - b. fissure
  - c. root
  - d. pleura
11. A section of the lung that receives its own tertiary bronchus is called the \_\_\_\_\_.
  - a. bronchopulmonary segment
  - b. pulmonary lobule
  - c. interpulmonary segment
  - d. respiratory segment
12. The \_\_\_\_\_ circulation picks up oxygen for cellular use and drops off carbon dioxide for removal from the body.
  - a. pulmonary
  - b. interlobular
  - c. respiratory
  - d. bronchial
13. The pleura that surrounds the lungs consists of two layers, the \_\_\_\_\_.
  - a. visceral and parietal pleurae.
  - b. mediastinum and parietal pleurae.
  - c. visceral and mediastinum pleurae.
  - d. none of the above
14. Which of the following processes does atmospheric pressure play a role in?
  - a. pulmonary ventilation
  - b. production of pulmonary surfactant
  - c. resistance
  - d. surface tension
15. A decrease in volume leads to a(n) \_\_\_\_\_ pressure.
  - a. decrease in
  - b. equalization of
  - c. increase in
  - d. zero
16. The pressure difference between the intra-alveolar and intrapleural pressures is called \_\_\_\_\_.
  - a. atmospheric pressure
  - b. pulmonary pressure
  - c. negative pressure
  - d. transpulmonary pressure
17. Gas flow decreases as \_\_\_\_\_ increases.
  - a. resistance
  - b. pressure
  - c. airway diameter
  - d. friction

- 18.** Contraction of the external intercostal muscles causes which of the following to occur?
- The diaphragm moves downward.
  - The rib cage is compressed.
  - The thoracic cavity volume decreases.
  - The ribs and sternum move upward.
- 19.** Which of the following prevents the alveoli from collapsing?
- residual volume
  - tidal volume
  - expiratory reserve volume
  - inspiratory reserve volume
- 20.** Gas moves from an area of \_\_\_\_\_ partial pressure to an area of \_\_\_\_\_ partial pressure.
- low; high
  - low; low
  - high; high
  - high; low
- 21.** When ventilation is not sufficient, which of the following occurs?
- The capillary constricts.
  - The capillary dilates.
  - The partial pressure of oxygen in the affected alveolus increases.
  - The bronchioles dilate.
- 22.** Gas exchange that occurs at the level of the tissues is called \_\_\_\_\_.
- external respiration
  - interpulmonary respiration
  - internal respiration
  - pulmonary ventilation
- 23.** The partial pressure of carbon dioxide is 45 mm Hg in the blood and 40 mm Hg in the alveoli. What happens to the carbon dioxide?
- It diffuses into the blood.
  - It diffuses into the alveoli.
  - The gradient is too small for carbon dioxide to diffuse.
  - It decomposes into carbon and oxygen.
- 24.** Oxyhemoglobin forms by a chemical reaction between which of the following?
- hemoglobin and carbon dioxide
  - carbonic anhydrase and carbon dioxide
  - hemoglobin and oxygen
  - carbonic anhydrase and oxygen
- 25.** Which of the following factors play a role in the oxygen–hemoglobin saturation/dissociation curve?
- temperature
  - pH
  - BPG
  - all of the above
- 26.** Which of the following occurs during the chloride shift?
- Chloride is removed from the erythrocyte.
  - Chloride is exchanged for bicarbonate.
  - Bicarbonate is removed from the erythrocyte.
  - Bicarbonate is removed from the blood.
- 27.** A low partial pressure of oxygen promotes hemoglobin binding to carbon dioxide. This is an example of the \_\_\_\_\_.
- Haldane effect
  - Bohr effect
  - Dalton’s law
  - Henry’s law
- 28.** Increased ventilation that results in an increase in blood pH is called \_\_\_\_\_.
- hyperventilation
  - hyperpnea
  - acclimatization
  - apnea
- 29.** Exercise can trigger symptoms of AMS due to which of the following?
- low partial pressure of oxygen
  - low atmospheric pressure
  - abnormal neural signals
  - small venous reserve of oxygen
- 30.** Which of the following stimulates the production of erythrocytes?
- AMS
  - high blood levels of carbon dioxide
  - low atmospheric pressure
  - erythropoietin
- 31.** The olfactory pits form from which of the following?
- mesoderm
  - cartilage
  - ectoderm
  - endoderm
- 32.** A full complement of mature alveoli are present by \_\_\_\_\_.
- early childhood, around 8 years of age
  - birth
  - 37 weeks
  - 16 weeks
- 33.** If a baby is born prematurely before type II cells produce sufficient pulmonary surfactant, which of the following might you expect?
- difficulty expressing fluid
  - difficulty inflating the lungs
  - difficulty with pulmonary capillary flow
  - no difficulty as type I cells can provide enough surfactant for normal breathing

- 34.** When do fetal breathing movements begin?
- around week 20
  - around week 37
  - around week 16
  - after birth
- 35.** What happens to the fluid that remains in the lungs after birth?
- It reduces the surface tension of the alveoli.
  - It is expelled shortly after birth.
  - It is absorbed shortly after birth.
  - It lubricates the pleurae.

## CRITICAL THINKING QUESTIONS

- 36.** Describe the three regions of the pharynx and their functions.
- 37.** If a person sustains an injury to the epiglottis, what would be the physiological result?
- 38.** Compare and contrast the conducting and respiratory zones.
- 39.** Compare and contrast the right and left lungs.
- 40.** Why are the pleurae not damaged during normal breathing?
- 41.** Describe what is meant by the term “lung compliance.”
- 42.** Outline the steps involved in quiet breathing.
- 43.** What is respiratory rate and how is it controlled?
- 44.** Compare and contrast Dalton’s law and Henry’s law.
- 45.** A smoker develops damage to several alveoli that then can no longer function. How does this affect gas exchange?
- 46.** Compare and contrast adult hemoglobin and fetal hemoglobin.
- 47.** Describe the relationship between the partial pressure of oxygen and the binding of oxygen to hemoglobin.
- 48.** Describe three ways in which carbon dioxide can be transported.
- 49.** Describe the neural factors involved in increasing ventilation during exercise.
- 50.** What is the major mechanism that results in acclimatization?
- 51.** During what timeframe does a fetus have enough mature structures to breathe on its own if born prematurely? Describe the other structures that develop during this phase.
- 52.** Describe fetal breathing movements and their purpose.



# 23 | THE DIGESTIVE SYSTEM



**Figure 23.1 Eating Apples** Eating may be one of the simple pleasures in life, but digesting even one apple requires the coordinated work of many organs. (credit: “Aimanness Photography”/Flickr)

## Introduction

### Chapter Objectives

After studying this chapter, you will be able to:

- List and describe the functional anatomy of the organs and accessory organs of the digestive system
- Discuss the processes and control of ingestion, propulsion, mechanical digestion, chemical digestion, absorption, and defecation
- Discuss the roles of the liver, pancreas, and gallbladder in digestion
- Compare and contrast the digestion of the three macronutrients

The digestive system is continually at work, yet people seldom appreciate the complex tasks it performs in a choreographed biologic symphony. Consider what happens when you eat an apple. Of course, you enjoy the apple’s taste as you chew it, but in the hours that follow, unless something goes amiss and you get a stomachache, you don’t notice that your digestive

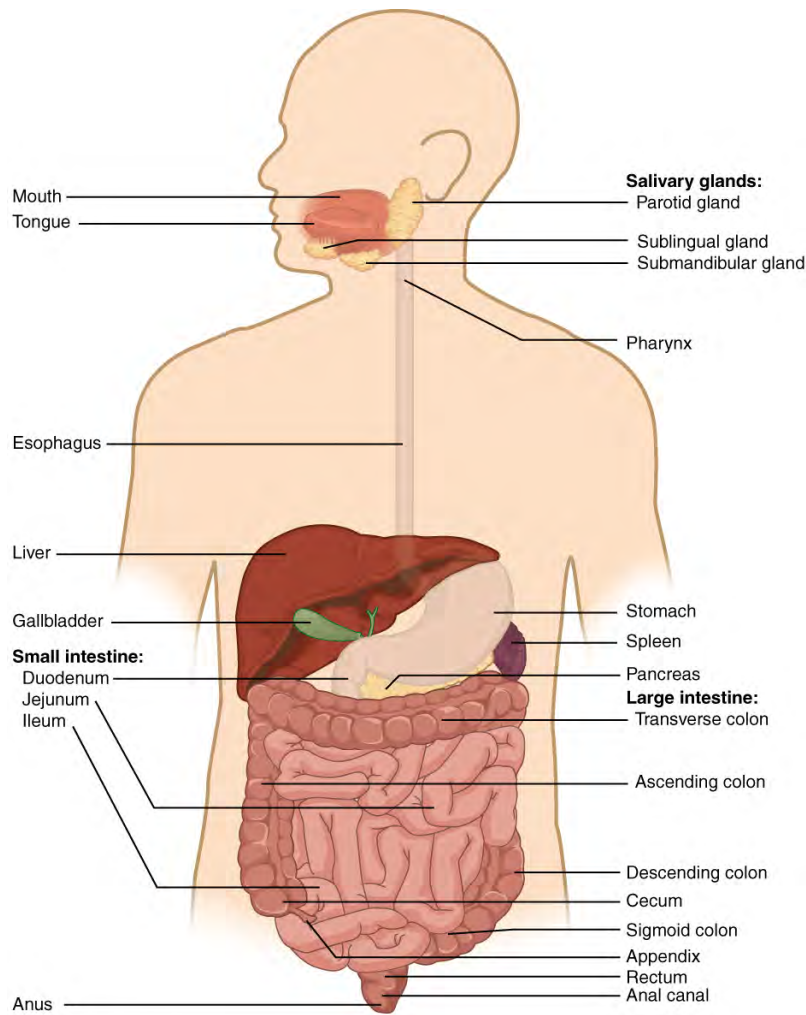
system is working. You may be taking a walk or studying or sleeping, having forgotten all about the apple, but your stomach and intestines are busy digesting it and absorbing its vitamins and other nutrients. By the time any waste material is excreted, the body has appropriated all it can use from the apple. In short, whether you pay attention or not, the organs of the digestive system perform their specific functions, allowing you to use the food you eat to keep you going. This chapter examines the structure and functions of these organs, and explores the mechanics and chemistry of the digestive processes.

## 23.1 | Overview of the Digestive System

By the end of this section, you will be able to:

- Identify the organs of the alimentary canal from proximal to distal, and briefly state their function
- Identify the accessory digestive organs and briefly state their function
- Describe the four fundamental tissue layers of the alimentary canal
- Contrast the contributions of the enteric and autonomic nervous systems to digestive system functioning
- Explain how the peritoneum anchors the digestive organs

The function of the digestive system is to break down the foods you eat, release their nutrients, and absorb those nutrients into the body. Although the small intestine is the workhorse of the system, where the majority of digestion occurs, and where most of the released nutrients are absorbed into the blood or lymph, each of the digestive system organs makes a vital contribution to this process (**Figure 23.2**).



**Figure 23.2 Components of the Digestive System** All digestive organs play integral roles in the life-sustaining process of digestion.

As is the case with all body systems, the digestive system does not work in isolation; it functions cooperatively with the other systems of the body. Consider for example, the interrelationship between the digestive and cardiovascular systems. Arteries supply the digestive organs with oxygen and processed nutrients, and veins drain the digestive tract. These intestinal veins, constituting the hepatic portal system, are unique; they do not return blood directly to the heart. Rather, this blood is diverted to the liver where its nutrients are off-loaded for processing before blood completes its circuit back to the heart. At the same time, the digestive system provides nutrients to the heart muscle and vascular tissue to support their functioning. The interrelationship of the digestive and endocrine systems is also critical. Hormones secreted by several endocrine glands, as well as endocrine cells of the pancreas, the stomach, and the small intestine, contribute to the control of digestion and nutrient metabolism. In turn, the digestive system provides the nutrients to fuel endocrine function. **Table 23.1** gives a quick glimpse at how these other systems contribute to the functioning of the digestive system.

### Contribution of Other Body Systems to the Digestive System

Body system	Benefits received by the digestive system
Cardiovascular	Blood supplies digestive organs with oxygen and processed nutrients
Endocrine	Endocrine hormones help regulate secretion in digestive glands and accessory organs

**Table 23.1**

## Contribution of Other Body Systems to the Digestive System

Body system	Benefits received by the digestive system
Integumentary	Skin helps protect digestive organs and synthesizes vitamin D for calcium absorption
Lymphatic	Mucosa-associated lymphoid tissue and other lymphatic tissue defend against entry of pathogens; lacteals absorb lipids; and lymphatic vessels transport lipids to bloodstream
Muscular	Skeletal muscles support and protect abdominal organs
Nervous	Sensory and motor neurons help regulate secretions and muscle contractions in the digestive tract
Respiratory	Respiratory organs provide oxygen and remove carbon dioxide
Skeletal	Bones help protect and support digestive organs
Urinary	Kidneys convert vitamin D into its active form, allowing calcium absorption in the small intestine

**Table 23.1**

## Digestive System Organs

The easiest way to understand the digestive system is to divide its organs into two main categories. The first group is the organs that make up the alimentary canal. Accessory digestive organs comprise the second group and are critical for orchestrating the breakdown of food and the assimilation of its nutrients into the body. Accessory digestive organs, despite their name, are critical to the function of the digestive system.

### Alimentary Canal Organs

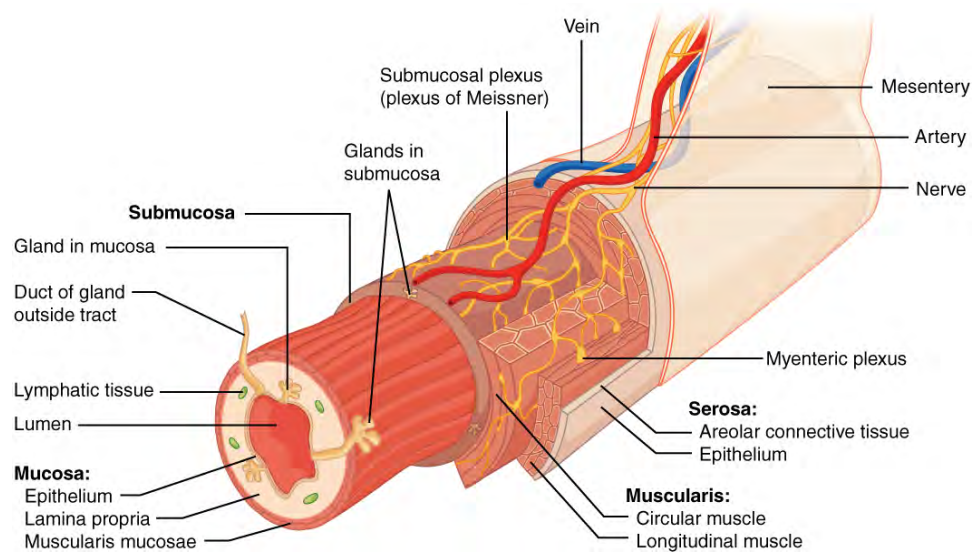
Also called the gastrointestinal (GI) tract or gut, the **alimentary canal** (aliment- = “to nourish”) is a one-way tube about 7.62 meters (25 feet) in length during life and closer to 10.67 meters (35 feet) in length when measured after death, once smooth muscle tone is lost. The main function of the organs of the alimentary canal is to nourish the body. This tube begins at the mouth and terminates at the anus. Between those two points, the canal is modified as the pharynx, esophagus, stomach, and small and large intestines to fit the functional needs of the body. Both the mouth and anus are open to the external environment; thus, food and wastes within the alimentary canal are technically considered to be outside the body. Only through the process of absorption do the nutrients in food enter into and nourish the body’s “inner space.”

### Accessory Structures

Each **accessory digestive organ** aids in the breakdown of food (**Figure 23.3**). Within the mouth, the teeth and tongue begin mechanical digestion, whereas the salivary glands begin chemical digestion. Once food products enter the small intestine, the gallbladder, liver, and pancreas release secretions—such as bile and enzymes—essential for digestion to continue. Together, these are called accessory organs because they sprout from the lining cells of the developing gut (mucosa) and augment its function; indeed, you could not live without their vital contributions, and many significant diseases result from their malfunction. Even after development is complete, they maintain a connection to the gut by way of ducts.

## Histology of the Alimentary Canal

Throughout its length, the alimentary tract is composed of the same four tissue layers; the details of their structural arrangements vary to fit their specific functions. Starting from the lumen and moving outwards, these layers are the mucosa, submucosa, muscularis, and serosa, which is continuous with the mesentery (see **Figure 23.3**).



**Figure 23.3 Layers of the Alimentary Canal** The wall of the alimentary canal has four basic tissue layers: the mucosa, submucosa, muscularis, and serosa.

The **mucosa** is referred to as a mucous membrane, because mucus production is a characteristic feature of gut epithelium. The membrane consists of epithelium, which is in direct contact with ingested food, and the lamina propria, a layer of connective tissue analogous to the dermis. In addition, the mucosa has a thin, smooth muscle layer, called the muscularis mucosa (not to be confused with the muscularis layer, described below).

**Epithelium**—In the mouth, pharynx, esophagus, and anal canal, the epithelium is primarily a non-keratinized, stratified squamous epithelium. In the stomach and intestines, it is a simple columnar epithelium. Notice that the epithelium is in direct contact with the lumen, the space inside the alimentary canal. Interspersed among its epithelial cells are goblet cells, which secrete mucus and fluid into the lumen, and enteroendocrine cells, which secrete hormones into the interstitial spaces between cells. Epithelial cells have a very brief lifespan, averaging from only a couple of days (in the mouth) to about a week (in the gut). This process of rapid renewal helps preserve the health of the alimentary canal, despite the wear and tear resulting from continued contact with foodstuffs.

**Lamina propria**—In addition to loose connective tissue, the lamina propria contains numerous blood and lymphatic vessels that transport nutrients absorbed through the alimentary canal to other parts of the body. The lamina propria also serves an immune function by housing clusters of lymphocytes, making up the mucosa-associated lymphoid tissue (MALT). These lymphocyte clusters are particularly substantial in the distal ileum where they are known as Peyer’s patches. When you consider that the alimentary canal is exposed to foodborne bacteria and other foreign matter, it is not hard to appreciate why the immune system has evolved a means of defending against the pathogens encountered within it.

**Muscularis mucosa**—This thin layer of smooth muscle is in a constant state of tension, pulling the mucosa of the stomach and small intestine into undulating folds. These folds dramatically increase the surface area available for digestion and absorption.

As its name implies, the **submucosa** lies immediately beneath the mucosa. A broad layer of dense connective tissue, it connects the overlying mucosa to the underlying muscularis. It includes blood and lymphatic vessels (which transport absorbed nutrients), and a scattering of submucosal glands that release digestive secretions. Additionally, it serves as a conduit for a dense branching network of nerves, the submucosal plexus, which functions as described below.

The third layer of the alimentary canal is the **muscularis** (also called the muscularis externa). The muscularis in the small intestine is made up of a double layer of smooth muscle: an inner circular layer and an outer longitudinal layer. The contractions of these layers promote mechanical digestion, expose more of the food to digestive chemicals, and move the food along the canal. In the most proximal and distal regions of the alimentary canal, including the mouth, pharynx, anterior part of the esophagus, and external anal sphincter, the muscularis is made up of skeletal muscle, which gives you voluntary control over swallowing and defecation. The basic two-layer structure found in the small intestine is modified in the organs proximal and distal to it. The stomach is equipped for its churning function by the addition of a third layer, the oblique muscle. While the colon has two layers like the small intestine, its longitudinal layer is segregated into three narrow parallel bands, the tenia coli, which make it look like a series of pouches rather than a simple tube.

The **serosa** is the portion of the alimentary canal superficial to the muscularis. Present only in the region of the alimentary canal within the abdominal cavity, it consists of a layer of visceral peritoneum overlying a layer of loose connective tissue. Instead of serosa, the mouth, pharynx, and esophagus have a dense sheath of collagen fibers called the adventitia. These tissues serve to hold the alimentary canal in place near the ventral surface of the vertebral column.

## Nerve Supply

As soon as food enters the mouth, it is detected by receptors that send impulses along the sensory neurons of cranial nerves. Without these nerves, not only would your food be without taste, but you would also be unable to feel either the food or the structures of your mouth, and you would be unable to avoid biting yourself as you chew, an action enabled by the motor branches of cranial nerves.

Intrinsic innervation of much of the alimentary canal is provided by the enteric nervous system, which runs from the esophagus to the anus, and contains approximately 100 million motor, sensory, and interneurons (unique to this system compared to all other parts of the peripheral nervous system). These enteric neurons are grouped into two plexuses. The **myenteric plexus** (plexus of Auerbach) lies in the muscularis layer of the alimentary canal and is responsible for **motility**, especially the rhythm and force of the contractions of the muscularis. The **submucosal plexus** (plexus of Meissner) lies in the submucosal layer and is responsible for regulating digestive secretions and reacting to the presence of food (see **Figure 23.3**).

Extrinsic innervations of the alimentary canal are provided by the autonomic nervous system, which includes both sympathetic and parasympathetic nerves. In general, sympathetic activation (the fight-or-flight response) restricts the activity of enteric neurons, thereby decreasing GI secretion and motility. In contrast, parasympathetic activation (the rest-and-digest response) increases GI secretion and motility by stimulating neurons of the enteric nervous system.

## Blood Supply

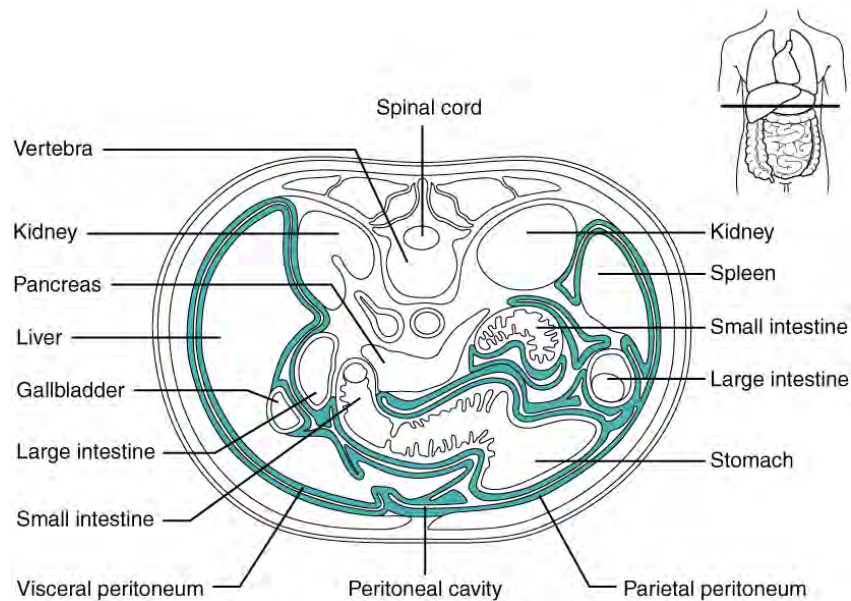
The blood vessels serving the digestive system have two functions. They transport the protein and carbohydrate nutrients absorbed by mucosal cells after food is digested in the lumen. Lipids are absorbed via lacteals, tiny structures of the lymphatic system. The blood vessels' second function is to supply the organs of the alimentary canal with the nutrients and oxygen needed to drive their cellular processes.

Specifically, the more anterior parts of the alimentary canal are supplied with blood by arteries branching off the aortic arch and thoracic aorta. Below this point, the alimentary canal is supplied with blood by arteries branching from the abdominal aorta. The celiac trunk services the liver, stomach, and duodenum, whereas the superior and inferior mesenteric arteries supply blood to the remaining small and large intestines.

The veins that collect nutrient-rich blood from the small intestine (where most absorption occurs) empty into the hepatic portal system. This venous network takes the blood into the liver where the nutrients are either processed or stored for later use. Only then does the blood drained from the alimentary canal viscera circulate back to the heart. To appreciate just how demanding the digestive process is on the cardiovascular system, consider that while you are “resting and digesting,” about one-fourth of the blood pumped with each heartbeat enters arteries serving the intestines.

## The Peritoneum

The digestive organs within the abdominal cavity are held in place by the peritoneum, a broad serous membranous sac made up of squamous epithelial tissue surrounded by connective tissue. It is composed of two different regions: the parietal peritoneum, which lines the abdominal wall, and the visceral peritoneum, which envelopes the abdominal organs (**Figure 23.4**). The peritoneal cavity is the space bounded by the visceral and parietal peritoneal surfaces. A few milliliters of watery fluid act as a lubricant to minimize friction between the serosal surfaces of the peritoneum.



**Figure 23.4 The Peritoneum** A cross-section of the abdomen shows the relationship between abdominal organs and the peritoneum (darker lines).

## Disorders OF THE...

### Digestive System: Peritonitis

Inflammation of the peritoneum is called peritonitis. Chemical peritonitis can develop any time the wall of the alimentary canal is breached, allowing the contents of the lumen entry into the peritoneal cavity. For example, when an ulcer perforates the stomach wall, gastric juices spill into the peritoneal cavity. Hemorrhagic peritonitis occurs after a ruptured tubal pregnancy or traumatic injury to the liver or spleen fills the peritoneal cavity with blood. Even more severe peritonitis is associated with bacterial infections seen with appendicitis, colonic diverticulitis, and pelvic inflammatory disease (infection of uterine tubes, usually by sexually transmitted bacteria). Peritonitis is life threatening and often results in emergency surgery to correct the underlying problem and intensive antibiotic therapy. When your great grandparents and even your parents were young, the mortality from peritonitis was high. Aggressive surgery, improvements in anesthesia safety, the advance of critical care expertise, and antibiotics have greatly improved the mortality rate from this condition. Even so, the mortality rate still ranges from 30 to 40 percent.

The visceral peritoneum includes multiple large folds that envelope various abdominal organs, holding them to the dorsal surface of the body wall. Within these folds are blood vessels, lymphatic vessels, and nerves that innervate the organs with which they are in contact, supplying their adjacent organs. The five major peritoneal folds are described in [Table 23.2](#). Note that during fetal development, certain digestive structures, including the first portion of the small intestine (called the duodenum), the pancreas, and portions of the large intestine (the ascending and descending colon, and the rectum) remain completely or partially posterior to the peritoneum. Thus, the location of these organs is described as **retroperitoneal**.

#### The Five Major Peritoneal Folds

Fold	Description
Greater omentum	Apron-like structure that lies superficial to the small intestine and transverse colon; a site of fat deposition in people who are overweight

**Table 23.2**

## The Five Major Peritoneal Folds

Fold	Description
Falciform ligament	Anchors the liver to the anterior abdominal wall and inferior border of the diaphragm
Lesser omentum	Suspends the stomach from the inferior border of the liver; provides a pathway for structures connecting to the liver
Mesentery	Vertical band of tissue anterior to the lumbar vertebrae and anchoring all of the small intestine except the initial portion (the duodenum)
Mesocolon	Attaches two portions of the large intestine (the transverse and sigmoid colon) to the posterior abdominal wall

**Table 23.2**

## 👉 Interactive LINK



By clicking on this [link \(http://openstaxcollege.org/l/fooddigestion\)](http://openstaxcollege.org/l/fooddigestion) you can watch a short video of what happens to the food you eat, as it passes from your mouth to your intestine. Along the way, note how the food changes consistency and form. How does this change in consistency facilitate your gaining nutrients from food?

## 23.2 | Digestive System Processes and Regulation

By the end of this section, you will be able to:

- Discuss six fundamental activities of the digestive system, giving an example of each
- Compare and contrast the neural and hormonal controls involved in digestion

The digestive system uses mechanical and chemical activities to break food down into absorbable substances during its journey through the digestive system. **Table 23.3** provides an overview of the basic functions of the digestive organs.

## Interactive LINK



Visit this [site \(http://openstaxcollege.org/l/fooddigestion2\)](http://openstaxcollege.org/l/fooddigestion2) for an overview of digestion of food in different regions of the digestive tract. Note the route of non-fat nutrients from the small intestine to their release as nutrients to the body.

### Functions of the Digestive Organs

Organ	Major functions	Other functions
Mouth	<ul style="list-style-type: none"> <li>Ingests food</li> <li>Chews and mixes food</li> <li>Begins chemical breakdown of carbohydrates</li> <li>Moves food into the pharynx</li> <li>Begins breakdown of lipids via lingual lipase</li> </ul>	<ul style="list-style-type: none"> <li>Moistens and dissolves food, allowing you to taste it</li> <li>Cleans and lubricates the teeth and oral cavity</li> <li>Has some antimicrobial activity</li> </ul>
Pharynx	<ul style="list-style-type: none"> <li>Propels food from the oral cavity to the esophagus</li> </ul>	<ul style="list-style-type: none"> <li>Lubricates food and passageways</li> </ul>
Esophagus	<ul style="list-style-type: none"> <li>Propels food to the stomach</li> </ul>	<ul style="list-style-type: none"> <li>Lubricates food and passageways</li> </ul>
Stomach	<ul style="list-style-type: none"> <li>Mixes and churns food with gastric juices to form chyme</li> <li>Begins chemical breakdown of proteins</li> <li>Releases food into the duodenum as chyme</li> <li>Absorbs some fat-soluble substances (for example, alcohol, aspirin)</li> <li>Possesses antimicrobial functions</li> </ul>	<ul style="list-style-type: none"> <li>Stimulates protein-digesting enzymes</li> <li>Secretes intrinsic factor required for vitamin B<sub>12</sub> absorption in small intestine</li> </ul>
Small intestine	<ul style="list-style-type: none"> <li>Mixes chyme with digestive juices</li> <li>Propels food at a rate slow enough for digestion and absorption</li> <li>Absorbs breakdown products of carbohydrates, proteins, lipids, and nucleic acids, along with vitamins, minerals, and water</li> <li>Performs physical digestion via segmentation</li> </ul>	<ul style="list-style-type: none"> <li>Provides optimal medium for enzymatic activity</li> </ul>

**Table 23.3**

## Functions of the Digestive Organs

Organ	Major functions	Other functions
Accessory organs	<p>Liver: produces bile salts, which emulsify lipids, aiding their digestion and absorption</p> <p>Gallbladder: stores, concentrates, and releases bile</p> <p>Pancreas: produces digestive enzymes and bicarbonate</p>	Bicarbonate-rich pancreatic juices help neutralize acidic chyme and provide optimal environment for enzymatic activity
Large intestine	<p>Further breaks down food residues</p> <p>Absorbs most residual water, electrolytes, and vitamins produced by enteric bacteria</p> <p>Propels feces toward rectum</p> <p>Eliminates feces</p>	<p>Food residue is concentrated and temporarily stored prior to defecation</p> <p>Mucus eases passage of feces through colon</p>

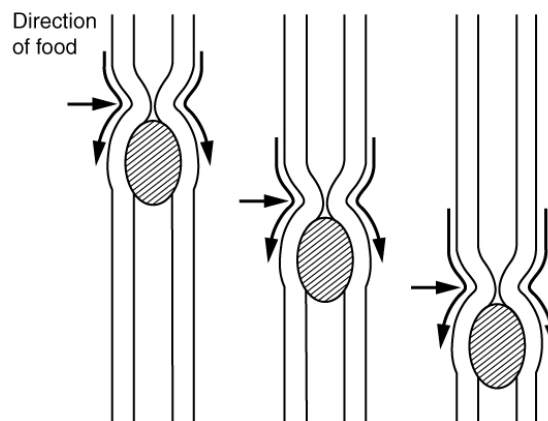
**Table 23.3**

## Digestive Processes

The processes of digestion include six activities: ingestion, propulsion, mechanical or physical digestion, chemical digestion, absorption, and defecation.

The first of these processes, **ingestion**, refers to the entry of food into the alimentary canal through the mouth. There, the food is chewed and mixed with saliva, which contains enzymes that begin breaking down the carbohydrates in the food plus some lipid digestion via lingual lipase. Chewing increases the surface area of the food and allows an appropriately sized bolus to be produced.

Food leaves the mouth when the tongue and pharyngeal muscles propel it into the esophagus. This act of swallowing, the last voluntary act until defecation, is an example of **propulsion**, which refers to the movement of food through the digestive tract. It includes both the voluntary process of swallowing and the involuntary process of peristalsis. **Peristalsis** consists of sequential, alternating waves of contraction and relaxation of alimentary wall smooth muscles, which act to propel food along (Figure 23.5). These waves also play a role in mixing food with digestive juices. Peristalsis is so powerful that foods and liquids you swallow enter your stomach even if you are standing on your head.



**Figure 23.5 Peristalsis** Peristalsis moves food through the digestive tract with alternating waves of muscle contraction and relaxation.

Digestion includes both mechanical and chemical processes. **Mechanical digestion** is a purely physical process that does not change the chemical nature of the food. Instead, it makes the food smaller to increase both surface area and mobility. It includes **mastication**, or chewing, as well as tongue movements that help break food into smaller bits and mix food with

saliva. Although there may be a tendency to think that mechanical digestion is limited to the first steps of the digestive process, it occurs after the food leaves the mouth, as well. The mechanical churning of food in the stomach serves to further break it apart and expose more of its surface area to digestive juices, creating an acidic “soup” called **chyme**. **Segmentation**, which occurs mainly in the small intestine, consists of localized contractions of circular muscle of the muscularis layer of the alimentary canal. These contractions isolate small sections of the intestine, moving their contents back and forth while continuously subdividing, breaking up, and mixing the contents. By moving food back and forth in the intestinal lumen, segmentation mixes food with digestive juices and facilitates absorption.

In **chemical digestion**, starting in the mouth, digestive secretions break down complex food molecules into their chemical building blocks (for example, proteins into separate amino acids). These secretions vary in composition, but typically contain water, various enzymes, acids, and salts. The process is completed in the small intestine.

Food that has been broken down is of no value to the body unless it enters the bloodstream and its nutrients are put to work. This occurs through the process of **absorption**, which takes place primarily within the small intestine. There, most nutrients are absorbed from the lumen of the alimentary canal into the bloodstream through the epithelial cells that make up the mucosa. Lipids are absorbed into lacteals and are transported via the lymphatic vessels to the bloodstream (the subclavian veins near the heart). The details of these processes will be discussed later.

In **defecation**, the final step in digestion, undigested materials are removed from the body as feces.

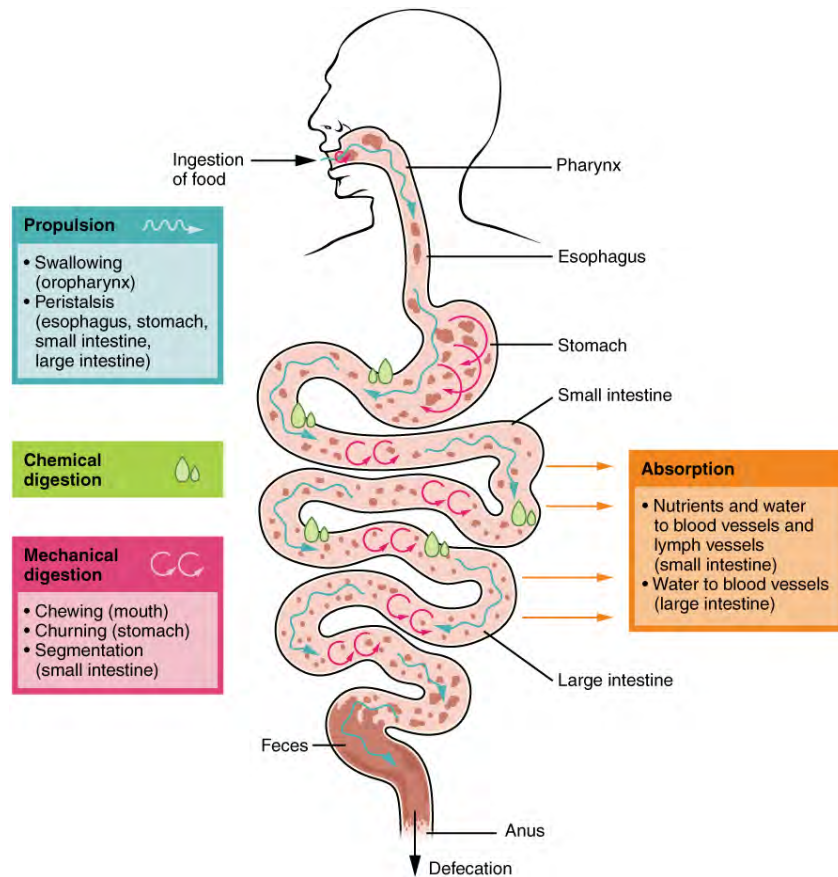
## **Ag**ng AND THE...

### **Digestive System: From Appetite Suppression to Constipation**

Age-related changes in the digestive system begin in the mouth and can affect virtually every aspect of the digestive system. Taste buds become less sensitive, so food isn't as appetizing as it once was. A slice of pizza is a challenge, not a treat, when you have lost teeth, your gums are diseased, and your salivary glands aren't producing enough saliva. Swallowing can be difficult, and ingested food moves slowly through the alimentary canal because of reduced strength and tone of muscular tissue. Neurosensory feedback is also dampened, slowing the transmission of messages that stimulate the release of enzymes and hormones.

Pathologies that affect the digestive organs—such as hiatal hernia, gastritis, and peptic ulcer disease—can occur at greater frequencies as you age. Problems in the small intestine may include duodenal ulcers, maldigestion, and malabsorption. Problems in the large intestine include hemorrhoids, diverticular disease, and constipation. Conditions that affect the function of accessory organs—and their abilities to deliver pancreatic enzymes and bile to the small intestine—include jaundice, acute pancreatitis, cirrhosis, and gallstones.

In some cases, a single organ is in charge of a digestive process. For example, ingestion occurs only in the mouth and defecation only in the anus. However, most digestive processes involve the interaction of several organs and occur gradually as food moves through the alimentary canal (**Figure 23.6**).



**Figure 23.6 Digestive Processes** The digestive processes are ingestion, propulsion, mechanical digestion, chemical digestion, absorption, and defecation.

Some chemical digestion occurs in the mouth. Some absorption can occur in the mouth and stomach, for example, alcohol and aspirin.

## Regulatory Mechanisms

Neural and endocrine regulatory mechanisms work to maintain the optimal conditions in the lumen needed for digestion and absorption. These regulatory mechanisms, which stimulate digestive activity through mechanical and chemical activity, are controlled both extrinsically and intrinsically.

### Neural Controls

The walls of the alimentary canal contain a variety of sensors that help regulate digestive functions. These include mechanoreceptors, chemoreceptors, and osmoreceptors, which are capable of detecting mechanical, chemical, and osmotic stimuli, respectively. For example, these receptors can sense when the presence of food has caused the stomach to expand, whether food particles have been sufficiently broken down, how much liquid is present, and the type of nutrients in the food (lipids, carbohydrates, and/or proteins). Stimulation of these receptors provokes an appropriate reflex that furthers the process of digestion. This may entail sending a message that activates the glands that secrete digestive juices into the lumen, or it may mean the stimulation of muscles within the alimentary canal, thereby activating peristalsis and segmentation that move food along the intestinal tract.

The walls of the entire alimentary canal are embedded with nerve plexuses that interact with the central nervous system and other nerve plexuses—either within the same digestive organ or in different ones. These interactions prompt several types of reflexes. Extrinsic nerve plexuses orchestrate long reflexes, which involve the central and autonomic nervous systems and work in response to stimuli from outside the digestive system. Short reflexes, on the other hand, are orchestrated by intrinsic nerve plexuses within the alimentary canal wall. These two plexuses and their connections were introduced earlier as the enteric nervous system. Short reflexes regulate activities in one area of the digestive tract and may coordinate local peristaltic movements and stimulate digestive secretions. For example, the sight, smell, and taste of food initiate long reflexes that begin with a sensory neuron delivering a signal to the medulla oblongata. The response to the signal is to

stimulate cells in the stomach to begin secreting digestive juices in preparation for incoming food. In contrast, food that distends the stomach initiates short reflexes that cause cells in the stomach wall to increase their secretion of digestive juices.

### Hormonal Controls

A variety of hormones are involved in the digestive process. The main digestive hormone of the stomach is gastrin, which is secreted in response to the presence of food. Gastrin stimulates the secretion of gastric acid by the parietal cells of the stomach mucosa. Other GI hormones are produced and act upon the gut and its accessory organs. Hormones produced by the duodenum include secretin, which stimulates a watery secretion of bicarbonate by the pancreas; cholecystokinin (CCK), which stimulates the secretion of pancreatic enzymes and bile from the liver and release of bile from the gallbladder; and gastric inhibitory peptide, which inhibits gastric secretion and slows gastric emptying and motility. These GI hormones are secreted by specialized epithelial cells, called endocrinocytes, located in the mucosal epithelium of the stomach and small intestine. These hormones then enter the bloodstream, through which they can reach their target organs.

## 23.3 | The Mouth, Pharynx, and Esophagus

By the end of this section, you will be able to:

- Describe the structures of the mouth, including its three accessory digestive organs
- Group the 32 adult teeth according to name, location, and function
- Describe the process of swallowing, including the roles of the tongue, upper esophageal sphincter, and epiglottis
- Trace the pathway food follows from ingestion into the mouth through release into the stomach

In this section, you will examine the anatomy and functions of the three main organs of the upper alimentary canal—the mouth, pharynx, and esophagus—as well as three associated accessory organs—the tongue, salivary glands, and teeth.

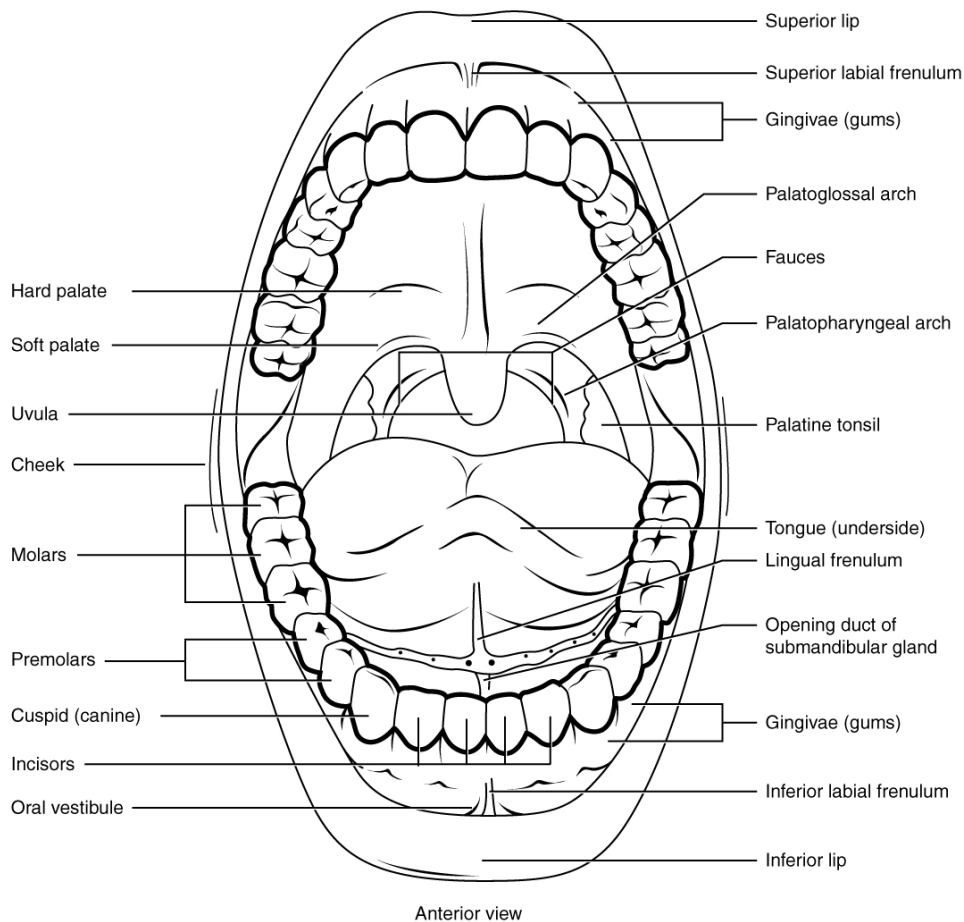
### The Mouth

The cheeks, tongue, and palate frame the mouth, which is also called the **oral cavity** (or buccal cavity). The structures of the mouth are illustrated in **Figure 23.7**.

At the entrance to the mouth are the lips, or **labia** (singular = labium). Their outer covering is skin, which transitions to a mucous membrane in the mouth proper. Lips are very vascular with a thin layer of keratin; hence, the reason they are "red." They have a huge representation on the cerebral cortex, which probably explains the human fascination with kissing! The lips cover the orbicularis oris muscle, which regulates what comes in and goes out of the mouth. The **labial frenulum** is a midline fold of mucous membrane that attaches the inner surface of each lip to the gum. The cheeks make up the oral cavity's sidewalls. While their outer covering is skin, their inner covering is mucous membrane. This membrane is made up of non-keratinized, stratified squamous epithelium. Between the skin and mucous membranes are connective tissue and buccinator muscles. The next time you eat some food, notice how the buccinator muscles in your cheeks and the orbicularis oris muscle in your lips contract, helping you keep the food from falling out of your mouth. Additionally, notice how these muscles work when you are speaking.

The pocket-like part of the mouth that is framed on the inside by the gums and teeth, and on the outside by the cheeks and lips is called the **oral vestibule**. Moving farther into the mouth, the opening between the oral cavity and throat (oropharynx) is called the **fauces** (like the kitchen "faucet"). The main open area of the mouth, or oral cavity proper, runs from the gums and teeth to the fauces.

When you are chewing, you do not find it difficult to breathe simultaneously. The next time you have food in your mouth, notice how the arched shape of the roof of your mouth allows you to handle both digestion and respiration at the same time. This arch is called the palate. The anterior region of the palate serves as a wall (or septum) between the oral and nasal cavities as well as a rigid shelf against which the tongue can push food. It is created by the maxillary and palatine bones of the skull and, given its bony structure, is known as the **hard palate**. If you run your tongue along the roof of your mouth, you'll notice that the hard palate ends in the posterior oral cavity, and the tissue becomes fleshier. This part of the palate, known as the **soft palate**, is composed mainly of skeletal muscle. You can therefore manipulate, subconsciously, the soft palate—for instance, to yawn, swallow, or sing (see **Figure 23.7**).



**Figure 23.7 Mouth** The mouth includes the lips, tongue, palate, gums, and teeth.

A fleshy bead of tissue called the uvula drops down from the center of the posterior edge of the soft palate. Although some have suggested that the uvula is a vestigial organ, it serves an important purpose. When you swallow, the soft palate and uvula move upward, helping to keep foods and liquid from entering the nasal cavity. Unfortunately, it can also contribute to the sound produced by snoring. Two muscular folds extend downward from the soft palate, on either side of the uvula. Toward the front, the **palatoglossal arch** lies next to the base of the tongue; behind it, the **palatopharyngeal arch** forms the superior and lateral margins of the fauces. Between these two arches are the palatine tonsils, clusters of lymphoid tissue that protect the pharynx. The lingual tonsils are located at the base of the tongue.

## The Tongue

Perhaps you have heard it said that the **tongue** is the strongest muscle in the body. Those who stake this claim cite its strength proportionate to its size. Although it is difficult to quantify the relative strength of different muscles, it remains indisputable that the tongue is a workhorse, facilitating ingestion, mechanical digestion, chemical digestion (lingual lipase), sensation (of taste, texture, and temperature of food), swallowing, and vocalization.

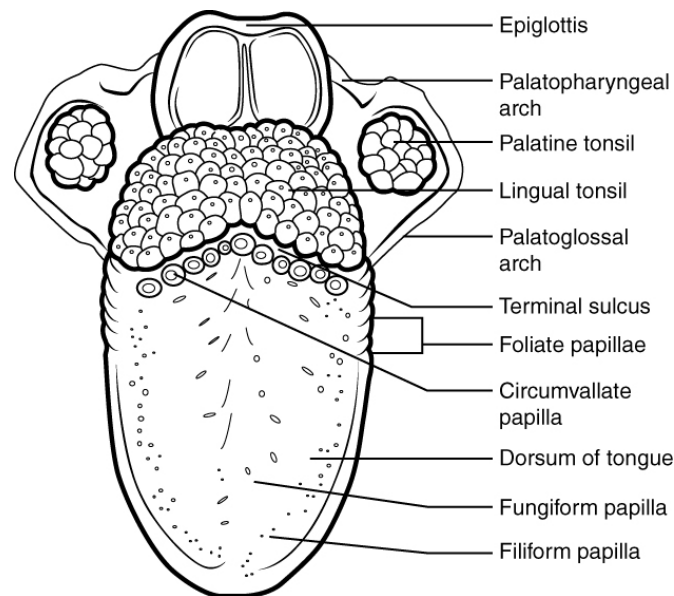
The tongue is attached to the mandible, the styloid processes of the temporal bones, and the hyoid bone. The hyoid is unique in that it only distantly/indirectly articulates with other bones. The tongue is positioned over the floor of the oral cavity. A medial septum extends the entire length of the tongue, dividing it into symmetrical halves.

Beneath its mucous membrane covering, each half of the tongue is composed of the same number and type of intrinsic and extrinsic skeletal muscles. The intrinsic muscles (those within the tongue) are the longitudinalis inferior, longitudinalis superior, transversus linguae, and verticalis linguae muscles. These allow you to change the size and shape of your tongue, as well as to stick it out, if you wish. Having such a flexible tongue facilitates both swallowing and speech.

As you learned in your study of the muscular system, the extrinsic muscles of the tongue are the mylohyoid, hyoglossus, styloglossus, and genioglossus muscles. These muscles originate outside the tongue and insert into connective tissues within the tongue. The mylohyoid is responsible for raising the tongue, the hyoglossus pulls it down and back, the styloglossus

pulls it up and back, and the genioglossus pulls it forward. Working in concert, these muscles perform three important digestive functions in the mouth: (1) position food for optimal chewing, (2) gather food into a **bolus** (rounded mass), and (3) position food so it can be swallowed.

The top and sides of the tongue are studded with papillae, extensions of lamina propria of the mucosa, which are covered in stratified squamous epithelium (**Figure 23.8**). Fungiform papillae, which are mushroom shaped, cover a large area of the tongue; they tend to be larger toward the rear of the tongue and smaller on the tip and sides. In contrast, filiform papillae are long and thin. Fungiform papillae contain taste buds, and filiform papillae have touch receptors that help the tongue move food around in the mouth. The filiform papillae create an abrasive surface that performs mechanically, much like a cat's rough tongue that is used for grooming. Lingual glands in the lamina propria of the tongue secrete mucus and a watery serous fluid that contains the enzyme **lingual lipase**, which plays a minor role in breaking down triglycerides but does not begin working until it is activated in the stomach. A fold of mucous membrane on the underside of the tongue, the **lingual frenulum**, tethers the tongue to the floor of the mouth. People with the congenital anomaly ankyloglossia, also known by the non-medical term “tongue tie,” have a lingual frenulum that is too short or otherwise malformed. Severe ankyloglossia can impair speech and must be corrected with surgery.



**Figure 23.8 Tongue** This superior view of the tongue shows the locations and types of lingual papillae.

## The Salivary Glands

Many small **salivary glands** are housed within the mucous membranes of the mouth and tongue. These minor exocrine glands are constantly secreting saliva, either directly into the oral cavity or indirectly through ducts, even while you sleep. In fact, an average of 1 to 1.5 liters of saliva is secreted each day. Usually just enough saliva is present to moisten the mouth and teeth. Secretion increases when you eat, because saliva is essential to moisten food and initiate the chemical breakdown of carbohydrates. Small amounts of saliva are also secreted by the labial glands in the lips. In addition, the buccal glands in the cheeks, palatal glands in the palate, and lingual glands in the tongue help ensure that all areas of the mouth are supplied with adequate saliva.

### The Major Salivary Glands

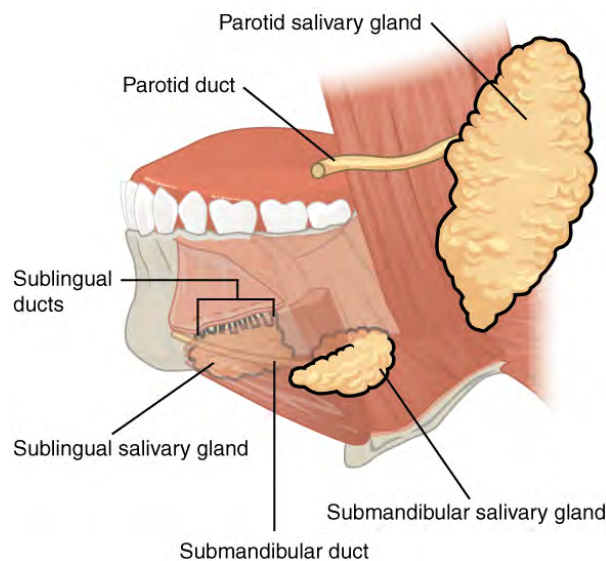
Outside the oral mucosa are three pairs of major salivary glands, which secrete the majority of saliva into ducts that open into the mouth:

- The **submandibular glands**, which are in the floor of the mouth, secrete saliva into the mouth through the submandibular ducts.
- The **sublingual glands**, which lie below the tongue, use the lesser sublingual ducts to secrete saliva into the oral cavity.
- The **parotid glands** lie between the skin and the masseter muscle, near the ears. They secrete saliva into the mouth through the parotid duct, which is located near the second upper molar tooth (**Figure 23.9**).

## Saliva

**Saliva** is essentially (95.5 percent) water. The remaining 4.5 percent is a complex mixture of ions, glycoproteins, enzymes, growth factors, and waste products. Perhaps the most important ingredient in saliva from the perspective of digestion is the enzyme **salivary amylase**, which initiates the breakdown of carbohydrates. Food does not spend enough time in the mouth to allow all the carbohydrates to break down, but salivary amylase continues acting until it is inactivated by stomach acids. Bicarbonate and phosphate ions function as chemical buffers, maintaining saliva at a pH between 6.35 and 6.85. Salivary mucus helps lubricate food, facilitating movement in the mouth, bolus formation, and swallowing. Saliva contains immunoglobulin A, which prevents microbes from penetrating the epithelium, and lysozyme, which makes saliva antimicrobial. Saliva also contains epidermal growth factor, which might have given rise to the adage “a mother’s kiss can heal a wound.”

Each of the major salivary glands secretes a unique formulation of saliva according to its cellular makeup. For example, the parotid glands secrete a watery solution that contains salivary amylase. The submandibular glands have cells similar to those of the parotid glands, as well as mucus-secreting cells. Therefore, saliva secreted by the submandibular glands also contains amylase but in a liquid thickened with mucus. The sublingual glands contain mostly mucous cells, and they secrete the thickest saliva with the least amount of salivary amylase.



**Figure 23.9 Salivary glands** The major salivary glands are located outside the oral mucosa and deliver saliva into the mouth through ducts.

# Homeostatic **IMBALANCES**

## The Parotid Glands: Mumps

Infections of the nasal passages and pharynx can attack any salivary gland. The parotid glands are the usual site of infection with the virus that causes mumps (paramyxovirus). Mumps manifests by enlargement and inflammation of the parotid glands, causing a characteristic swelling between the ears and the jaw. Symptoms include fever and throat pain, which can be severe when swallowing acidic substances such as orange juice.

In about one-third of men who are past puberty, mumps also causes testicular inflammation, typically affecting only one testis and rarely resulting in sterility. With the increasing use and effectiveness of mumps vaccines, the incidence of mumps has decreased dramatically. According to the U.S. Centers for Disease Control and Prevention (CDC), the number of mumps cases dropped from more than 150,000 in 1968 to fewer than 1700 in 1993 to only 11 reported cases in 2011.

## Regulation of Salivation

The autonomic nervous system regulates **salivation** (the secretion of saliva). In the absence of food, parasympathetic stimulation keeps saliva flowing at just the right level for comfort as you speak, swallow, sleep, and generally go about life. Over-salivation can occur, for example, if you are stimulated by the smell of food, but that food is not available for you to eat. Drooling is an extreme instance of the overproduction of saliva. During times of stress, such as before speaking in public, sympathetic stimulation takes over, reducing salivation and producing the symptom of dry mouth often associated with anxiety. When you are dehydrated, salivation is reduced, causing the mouth to feel dry and prompting you to take action to quench your thirst.

Salivation can be stimulated by the sight, smell, and taste of food. It can even be stimulated by thinking about food. You might notice whether reading about food and salivation right now has had any effect on your production of saliva.

How does the salivation process work while you are eating? Food contains chemicals that stimulate taste receptors on the tongue, which send impulses to the superior and inferior salivatory nuclei in the brain stem. These two nuclei then send back parasympathetic impulses through fibers in the glossopharyngeal and facial nerves, which stimulate salivation. Even after you swallow food, salivation is increased to cleanse the mouth and to water down and neutralize any irritating chemical remnants, such as that hot sauce in your burrito. Most saliva is swallowed along with food and is reabsorbed, so that fluid is not lost.

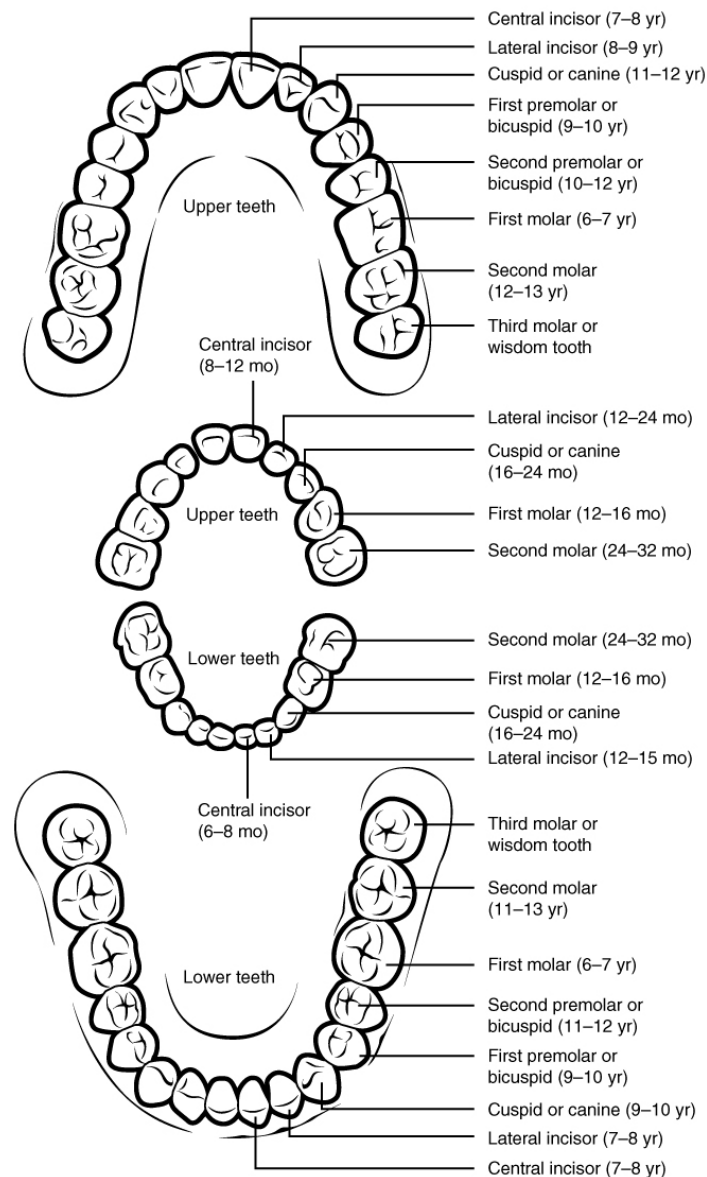
## The Teeth

The teeth, or **dentes** (singular = dens), are organs similar to bones that you use to tear, grind, and otherwise mechanically break down food.

### Types of Teeth

During the course of your lifetime, you have two sets of teeth (one set of teeth is a **dentition**). Your 20 **deciduous teeth**, or baby teeth, first begin to appear at about 6 months of age. Between approximately age 6 and 12, these teeth are replaced by 32 **permanent teeth**. Moving from the center of the mouth toward the side, these are as follows (**Figure 23.10**):

- The eight **incisors**, four top and four bottom, are the sharp front teeth you use for biting into food.
- The four **cuspid**s (or canines) flank the incisors and have a pointed edge (cusp) to tear up food. These fang-like teeth are superb for piercing tough or fleshy foods.
- Posterior to the cuspid are the eight **premolars** (or bicuspid)s, which have an overall flatter shape with two rounded cusps useful for mashing foods.
- The most posterior and largest are the 12 **molars**, which have several pointed cusps used to crush food so it is ready for swallowing. The third members of each set of three molars, top and bottom, are commonly referred to as the wisdom teeth, because their eruption is commonly delayed until early adulthood. It is not uncommon for wisdom teeth to fail to erupt; that is, they remain impacted. In these cases, the teeth are typically removed by orthodontic surgery.



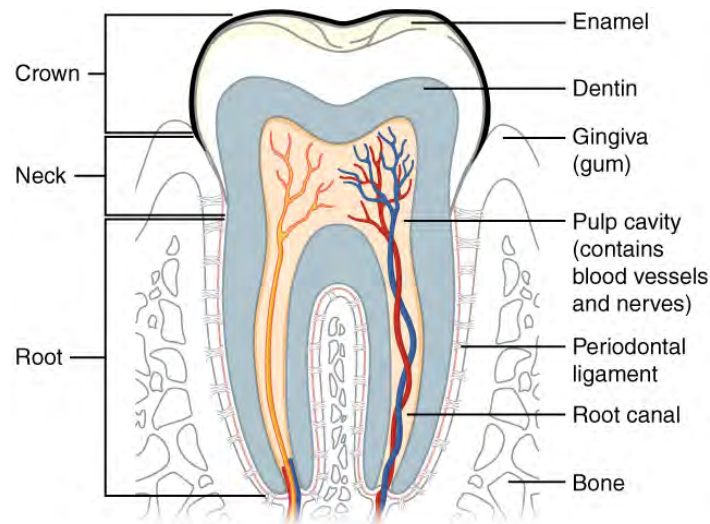
**Figure 23.10 Permanent and Deciduous Teeth** This figure of two human dentitions shows the arrangement of teeth in the maxilla and mandible, and the relationship between the deciduous and permanent teeth.

### Anatomy of a Tooth

The teeth are secured in the alveolar processes (sockets) of the maxilla and the mandible. **Gingivae** (commonly called the gums) are soft tissues that line the alveolar processes and surround the necks of the teeth. Teeth are also held in their sockets by a connective tissue called the periodontal ligament.

The two main parts of a tooth are the **crown**, which is the portion projecting above the gum line, and the **root**, which is embedded within the maxilla and mandible. Both parts contain an inner **pulp cavity**, containing loose connective tissue through which run nerves and blood vessels. The region of the pulp cavity that runs through the root of the tooth is called the root canal. Surrounding the pulp cavity is **dentin**, a bone-like tissue. In the root of each tooth, the dentin is covered by an even harder bone-like layer called **cementum**. In the crown of each tooth, the dentin is covered by an outer layer of **enamel**, the hardest substance in the body (**Figure 23.11**).

Although enamel protects the underlying dentin and pulp cavity, it is still nonetheless susceptible to mechanical and chemical erosion, or what is known as tooth decay. The most common form, dental caries (cavities) develops when colonies of bacteria feeding on sugars in the mouth release acids that cause soft tissue inflammation and degradation of the calcium crystals of the enamel. The digestive functions of the mouth are summarized in **Table 23.4**.



**Figure 23.11 The Structure of the Tooth** This longitudinal section through a molar in its alveolar socket shows the relationships between enamel, dentin, and pulp.

### Digestive Functions of the Mouth

Structure	Action	Outcome
Lips and cheeks	Confine food between teeth	Food is chewed evenly during mastication
Salivary glands	Secrete saliva	Moisten and lubricate the lining of the mouth and pharynx Moisten, soften, and dissolve food Clean the mouth and teeth Salivary amylase breaks down starch
Tongue's extrinsic muscles	Move tongue sideways, and in and out	Manipulate food for chewing Shape food into a bolus Manipulate food for swallowing
Tongue's intrinsic muscles	Change tongue shape	Manipulate food for swallowing
Taste buds	Sense food in mouth and sense taste	Nerve impulses from taste buds are conducted to salivary nuclei in the brain stem and then to salivary glands, stimulating saliva secretion
Lingual glands	Secrete lingual lipase	Activated in the stomach Break down triglycerides into fatty acids and diglycerides
Teeth	Shred and crush food	Break down solid food into smaller particles for deglutition

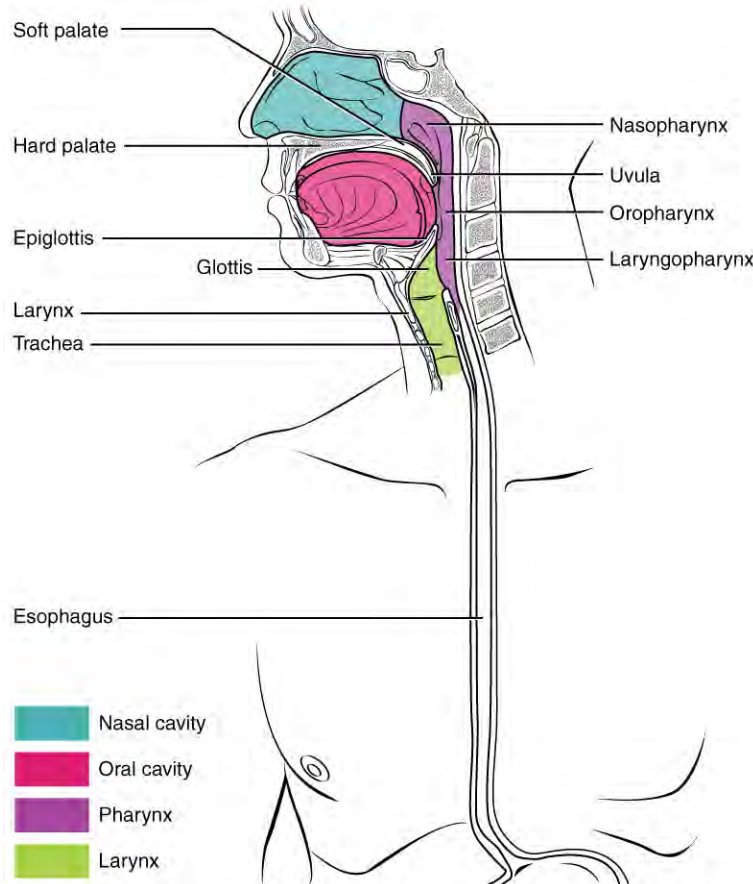
**Table 23.4**

### The Pharynx

The **pharynx** (throat) is involved in both digestion and respiration. It receives food and air from the mouth, and air from the

nasal cavities. When food enters the pharynx, involuntary muscle contractions close off the air passageways.

A short tube of skeletal muscle lined with a mucous membrane, the pharynx runs from the posterior oral and nasal cavities to the opening of the esophagus and larynx. It has three subdivisions. The most superior, the nasopharynx, is involved only in breathing and speech. The other two subdivisions, the **oropharynx** and the **laryngopharynx**, are used for both breathing and digestion. The oropharynx begins inferior to the nasopharynx and is continuous below with the laryngopharynx (**Figure 23.12**). The inferior border of the laryngopharynx connects to the esophagus, whereas the anterior portion connects to the larynx, allowing air to flow into the bronchial tree.



**Figure 23.12 Pharynx** The pharynx runs from the nostrils to the esophagus and the larynx.

Histologically, the wall of the oropharynx is similar to that of the oral cavity. The mucosa includes a stratified squamous epithelium that is endowed with mucus-producing glands. During swallowing, the elevator skeletal muscles of the pharynx contract, raising and expanding the pharynx to receive the bolus of food. Once received, these muscles relax and the constrictor muscles of the pharynx contract, forcing the bolus into the esophagus and initiating peristalsis.

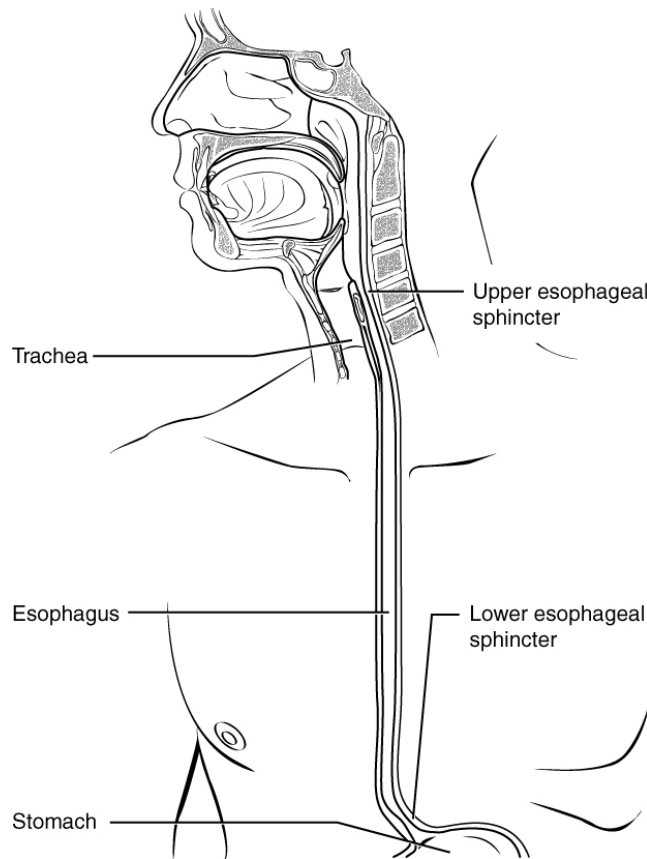
Usually during swallowing, the soft palate and uvula rise reflexively to close off the entrance to the nasopharynx. At the same time, the larynx is pulled superiorly and the cartilaginous epiglottis, its most superior structure, folds inferiorly, covering the glottis (the opening to the larynx); this process effectively blocks access to the trachea and bronchi. When the food “goes down the wrong way,” it goes into the trachea. When food enters the trachea, the reaction is to cough, which usually forces the food up and out of the trachea, and back into the pharynx.

## The Esophagus

The **esophagus** is a muscular tube that connects the pharynx to the stomach. It is approximately 25.4 cm (10 in) in length, located posterior to the trachea, and remains in a collapsed form when not engaged in swallowing. As you can see in **Figure 23.13**, the esophagus runs a mainly straight route through the mediastinum of the thorax. To enter the abdomen, the esophagus penetrates the diaphragm through an opening called the esophageal hiatus.

## Passage of Food through the Esophagus

The **upper esophageal sphincter**, which is continuous with the inferior pharyngeal constrictor, controls the movement of food from the pharynx into the esophagus. The upper two-thirds of the esophagus consists of both smooth and skeletal muscle fibers, with the latter fading out in the bottom third of the esophagus. Rhythmic waves of peristalsis, which begin in the upper esophagus, propel the bolus of food toward the stomach. Meanwhile, secretions from the esophageal mucosa lubricate the esophagus and food. Food passes from the esophagus into the stomach at the **lower esophageal sphincter** (also called the gastroesophageal or cardiac sphincter). Recall that sphincters are muscles that surround tubes and serve as valves, closing the tube when the sphincters contract and opening it when they relax. The lower esophageal sphincter relaxes to let food pass into the stomach, and then contracts to prevent stomach acids from backing up into the esophagus. Surrounding this sphincter is the muscular diaphragm, which helps close off the sphincter when no food is being swallowed. When the lower esophageal sphincter does not completely close, the stomach's contents can reflux (that is, back up into the esophagus), causing heartburn or gastroesophageal reflux disease (GERD).



**Figure 23.13 Esophagus** The upper esophageal sphincter controls the movement of food from the pharynx to the esophagus. The lower esophageal sphincter controls the movement of food from the esophagus to the stomach.

## Histology of the Esophagus

The mucosa of the esophagus is made up of an epithelial lining that contains non-keratinized, stratified squamous epithelium, with a layer of basal and parabasal cells. This epithelium protects against erosion from food particles. The mucosa's lamina propria contains mucus-secreting glands. The muscularis layer changes according to location: In the upper third of the esophagus, the muscularis is skeletal muscle. In the middle third, it is both skeletal and smooth muscle. In the lower third, it is smooth muscle. As mentioned previously, the most superficial layer of the esophagus is called the adventitia, not the serosa. In contrast to the stomach and intestines, the loose connective tissue of the adventitia is not covered by a fold of visceral peritoneum. The digestive functions of the esophagus are identified in **Table 23.5**.

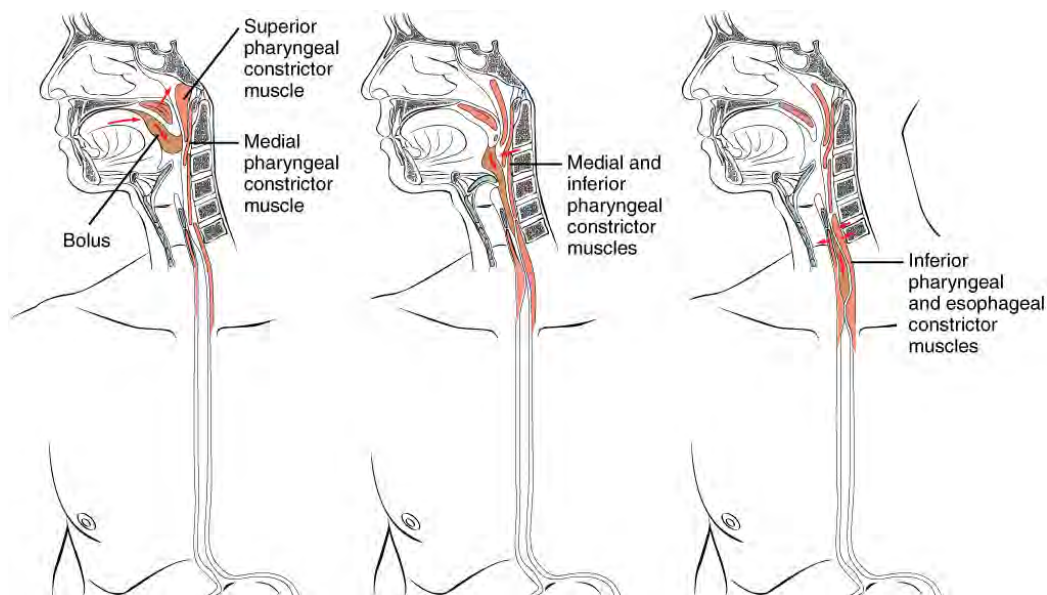
## Digestive Functions of the Esophagus

Action	Outcome
Upper esophageal sphincter relaxation	Allows the bolus to move from the laryngopharynx to the esophagus
Peristalsis	Propels the bolus through the esophagus
Lower esophageal sphincter relaxation	Allows the bolus to move from the esophagus into the stomach and prevents chime from entering the esophagus
Mucus secretion	Lubricates the esophagus, allowing easy passage of the bolus

**Table 23.5**

## Deglutition

**Deglutition** is another word for swallowing—the movement of food from the mouth to the stomach. The entire process takes about 4 to 8 seconds for solid or semisolid food, and about 1 second for very soft food and liquids. Although this sounds quick and effortless, deglutition is, in fact, a complex process that involves both the skeletal muscle of the tongue and the muscles of the pharynx and esophagus. It is aided by the presence of mucus and saliva. There are three stages in deglutition: the voluntary phase, the pharyngeal phase, and the esophageal phase (**Figure 23.14**). The autonomic nervous system controls the latter two phases.



**Figure 23.14 Deglutition** Deglutition includes the voluntary phase and two involuntary phases: the pharyngeal phase and the esophageal phase.

### The Voluntary Phase

The **voluntary phase** of deglutition (also known as the oral or buccal phase) is so called because you can control when you swallow food. In this phase, chewing has been completed and swallowing is set in motion. The tongue moves upward and backward against the palate, pushing the bolus to the back of the oral cavity and into the oropharynx. Other muscles keep the mouth closed and prevent food from falling out. At this point, the two involuntary phases of swallowing begin.

### The Pharyngeal Phase

In the pharyngeal phase, stimulation of receptors in the oropharynx sends impulses to the deglutition center (a collection of neurons that controls swallowing) in the medulla oblongata. Impulses are then sent back to the uvula and soft palate, causing them to move upward and close off the nasopharynx. The laryngeal muscles also constrict to prevent aspiration of food into the trachea. At this point, deglutition apnea takes place, which means that breathing ceases for a very brief time.

Contractions of the pharyngeal constrictor muscles move the bolus through the oropharynx and laryngopharynx. Relaxation of the upper esophageal sphincter then allows food to enter the esophagus.

### The Esophageal Phase

The entry of food into the esophagus marks the beginning of the esophageal phase of deglutition and the initiation of peristalsis. As in the previous phase, the complex neuromuscular actions are controlled by the medulla oblongata. Peristalsis propels the bolus through the esophagus and toward the stomach. The circular muscle layer of the muscularis contracts, pinching the esophageal wall and forcing the bolus forward. At the same time, the longitudinal muscle layer of the muscularis also contracts, shortening this area and pushing out its walls to receive the bolus. In this way, a series of contractions keeps moving food toward the stomach. When the bolus nears the stomach, distention of the esophagus initiates a short reflex relaxation of the lower esophageal sphincter that allows the bolus to pass into the stomach. During the esophageal phase, esophageal glands secrete mucus that lubricates the bolus and minimizes friction.



Watch this [animation \(http://openstaxcollege.org/l/swallowing\)](http://openstaxcollege.org/l/swallowing) to see how swallowing is a complex process that involves the nervous system to coordinate the actions of upper respiratory and digestive activities. During which stage of swallowing is there a risk of food entering respiratory pathways and how is this risk blocked?

## 23.4 | The Stomach

By the end of this section, you will be able to:

- Label on a diagram the four main regions of the stomach, its curvatures, and its sphincter
- Identify the four main types of secreting cells in gastric glands, and their important products
- Explain why the stomach does not digest itself
- Describe the mechanical and chemical digestion of food entering the stomach

Although a minimal amount of carbohydrate digestion occurs in the mouth, chemical digestion really gets underway in the stomach. An expansion of the alimentary canal that lies immediately inferior to the esophagus, the stomach links the esophagus to the first part of the small intestine (the duodenum) and is relatively fixed in place at its esophageal and duodenal ends. In between, however, it can be a highly active structure, contracting and continually changing position and size. These contractions provide mechanical assistance to digestion. The empty stomach is only about the size of your fist, but can stretch to hold as much as 4 liters of food and fluid, or more than 75 times its empty volume, and then return to its resting size when empty. Although you might think that the size of a person's stomach is related to how much food that individual consumes, body weight does not correlate with stomach size. Rather, when you eat greater quantities of food—such as at holiday dinner—you stretch the stomach more than when you eat less.

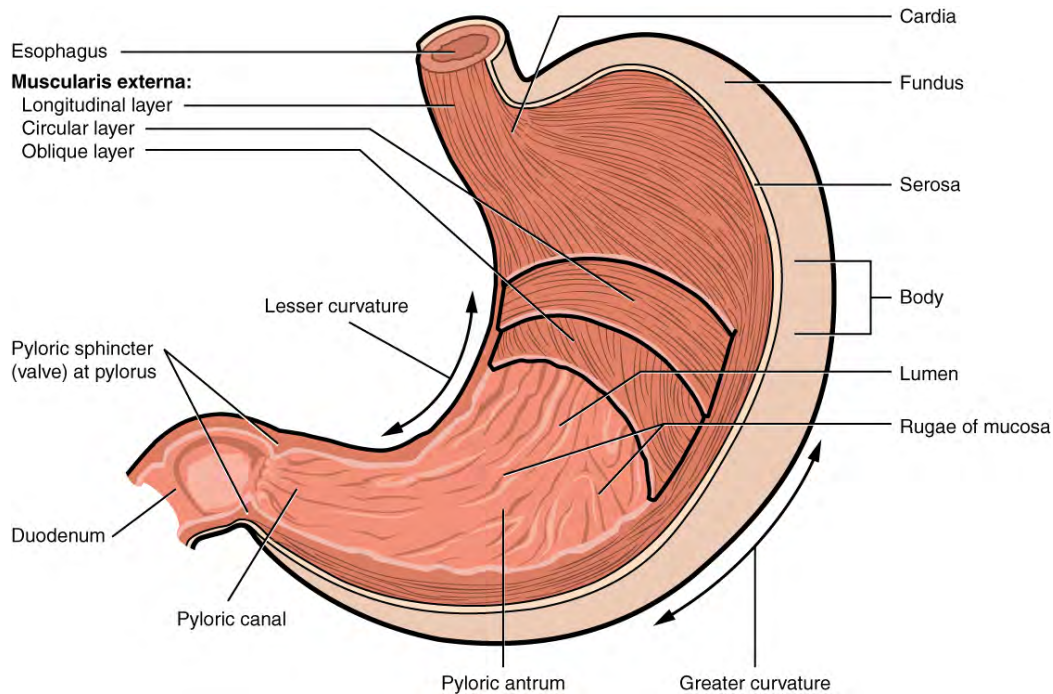
Popular culture tends to refer to the stomach as the location where all digestion takes place. Of course, this is not true. An important function of the stomach is to serve as a temporary holding chamber. You can ingest a meal far more quickly than it can be digested and absorbed by the small intestine. Thus, the stomach holds food and parses only small amounts into the small intestine at a time. Foods are not processed in the order they are eaten; rather, they are mixed together with digestive juices in the stomach until they are converted into chyme, which is released into the small intestine.

As you will see in the sections that follow, the stomach plays several important roles in chemical digestion, including the

continued digestion of carbohydrates and the initial digestion of proteins and triglycerides. Little if any nutrient absorption occurs in the stomach, with the exception of the negligible amount of nutrients in alcohol.

## Structure

There are four main regions in the **stomach**: the cardia, fundus, body, and pylorus (**Figure 23.15**). The **cardia** (or cardiac region) is the point where the esophagus connects to the stomach and through which food passes into the stomach. Located inferior to the diaphragm, above and to the left of the cardia, is the dome-shaped **fundus**. Below the fundus is the **body**, the main part of the stomach. The funnel-shaped **pylorus** connects the stomach to the duodenum. The wider end of the funnel, the **pyloric antrum**, connects to the body of the stomach. The narrower end is called the **pyloric canal**, which connects to the duodenum. The smooth muscle **pyloric sphincter** is located at this latter point of connection and controls stomach emptying. In the absence of food, the stomach deflates inward, and its mucosa and submucosa fall into a large fold called a **ruga**.

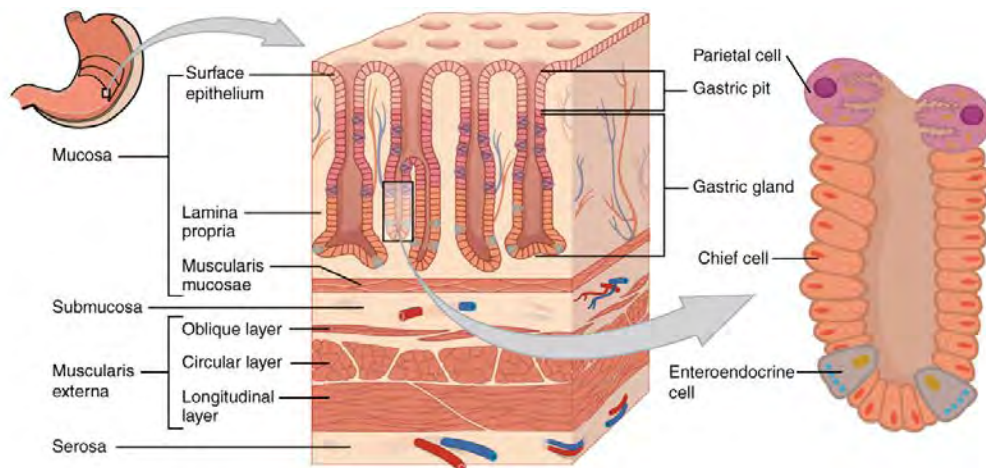


**Figure 23.15 Stomach** The stomach has four major regions: the cardia, fundus, body, and pylorus. The addition of an inner oblique smooth muscle layer gives the muscularis the ability to vigorously churn and mix food.

The convex lateral surface of the stomach is called the greater curvature; the concave medial border is the lesser curvature. The stomach is held in place by the lesser omentum, which extends from the liver to the lesser curvature, and the greater omentum, which runs from the greater curvature to the posterior abdominal wall.

## Histology

The wall of the stomach is made of the same four layers as most of the rest of the alimentary canal, but with adaptations to the mucosa and muscularis for the unique functions of this organ. In addition to the typical circular and longitudinal smooth muscle layers, the muscularis has an inner oblique smooth muscle layer (**Figure 23.16**). As a result, in addition to moving food through the canal, the stomach can vigorously churn food, mechanically breaking it down into smaller particles.



**Figure 23.16 Histology of the Stomach** The stomach wall is adapted for the functions of the stomach. In the epithelium, gastric pits lead to gastric glands that secrete gastric juice. The gastric glands (one gland is shown enlarged on the right) contain different types of cells that secrete a variety of enzymes, including hydrochloride acid, which activates the protein-digesting enzyme pepsin.

The stomach mucosa's epithelial lining consists only of surface mucus cells, which secrete a protective coat of alkaline mucus. A vast number of **gastric pits** dot the surface of the epithelium, giving it the appearance of a well-used pincushion, and mark the entry to each **gastric gland**, which secretes a complex digestive fluid referred to as gastric juice.

Although the walls of the gastric pits are made up primarily of mucus cells, the gastric glands are made up of different types of cells. The glands of the cardia and pylorus are composed primarily of mucus-secreting cells. Cells that make up the pyloric antrum secrete mucus and a number of hormones, including the majority of the stimulatory hormone, **gastrin**. The much larger glands of the fundus and body of the stomach, the site of most chemical digestion, produce most of the gastric secretions. These glands are made up of a variety of secretory cells. These include parietal cells, chief cells, mucous neck cells, and enteroendocrine cells.

**Parietal cells**—Located primarily in the middle region of the gastric glands are **parietal cells**, which are among the most highly differentiated of the body's epithelial cells. These relatively large cells produce both **hydrochloric acid (HCl)** and **intrinsic factor**. HCl is responsible for the high acidity (pH 1.5 to 3.5) of the stomach contents and is needed to activate the protein-digesting enzyme, pepsin. The acidity also kills much of the bacteria you ingest with food and helps to denature proteins, making them more available for enzymatic digestion. Intrinsic factor is a glycoprotein necessary for the absorption of vitamin B<sub>12</sub> in the small intestine.

**Chief cells**—Located primarily in the basal regions of gastric glands are **chief cells**, which secrete **pepsinogen**, the inactive proenzyme form of pepsin. HCl is necessary for the conversion of pepsinogen to pepsin.

**Mucous neck cells**—Gastric glands in the upper part of the stomach contain **mucous neck cells** that secrete thin, acidic mucus that is much different from the mucus secreted by the goblet cells of the surface epithelium. The role of this mucus is not currently known.

**Enteroendocrine cells**—Finally, **enteroendocrine cells** found in the gastric glands secrete various hormones into the interstitial fluid of the lamina propria. These include gastrin, which is released mainly by enteroendocrine **G cells**.

**Table 23.6** describes the digestive functions of important hormones secreted by the stomach.

## Interactive LINK



Watch this **animation** (<http://openstaxcollege.org/l/stomach1>) that depicts the structure of the stomach and how this structure functions in the initiation of protein digestion. This view of the stomach shows the characteristic rugae. What is the function of these rugae?

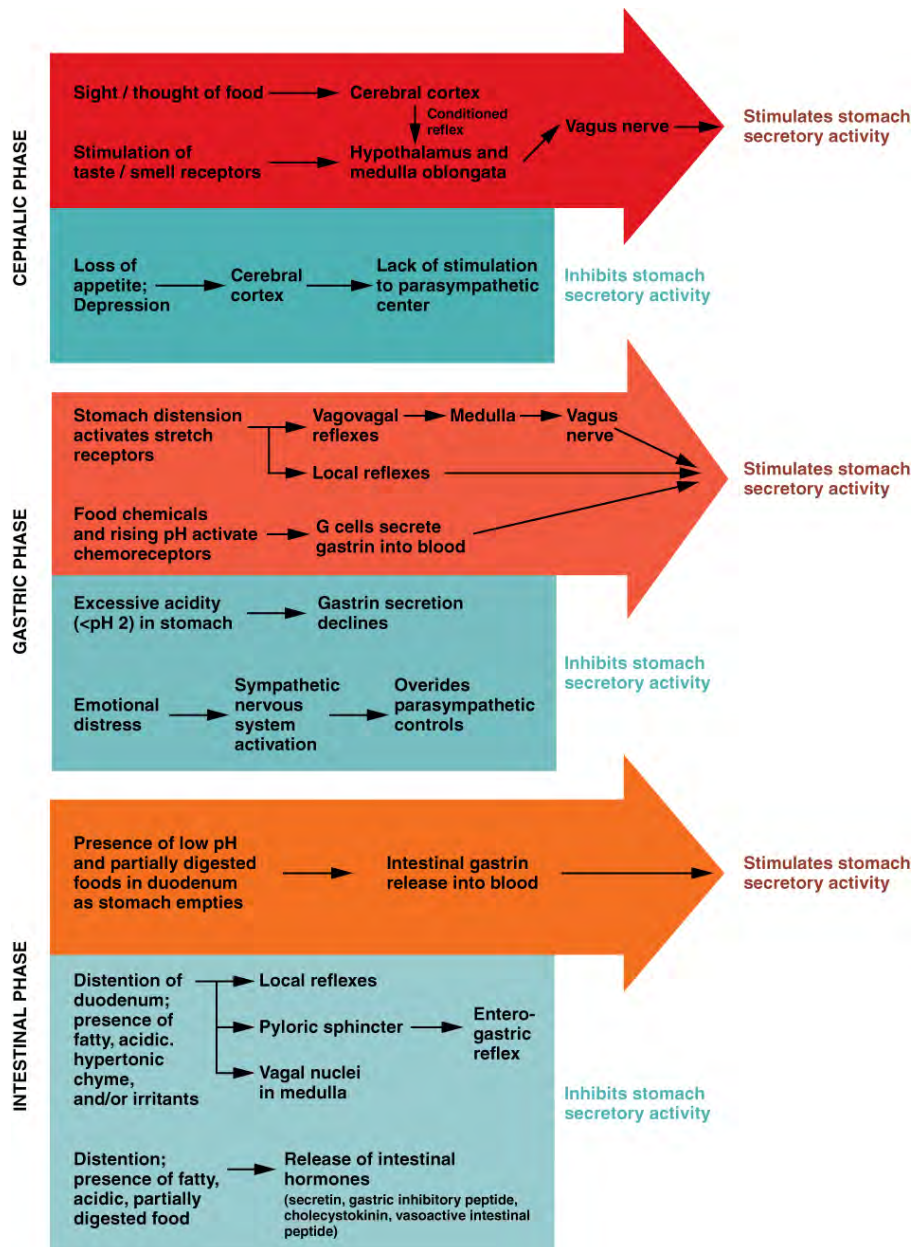
### Hormones Secreted by the Stomach

Hormone	Production site	Production stimulus	Target organ	Action
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Stomach	Increases secretion by gastric glands; promotes gastric emptying
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Small intestine	Promotes intestinal muscle contraction
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Ileocecal valve	Relaxes valve
Gastrin	Stomach mucosa, mainly G cells of the pyloric antrum	Presence of peptides and amino acids in stomach	Large intestine	Triggers mass movements
Ghrelin	Stomach mucosa, mainly fundus	Fasting state (levels increase just prior to meals)	Hypothalamus	Regulates food intake, primarily by stimulating hunger and satiety
Histamine	Stomach mucosa	Presence of food in the stomach	Stomach	Stimulates parietal cells to release HCl
Serotonin	Stomach mucosa	Presence of food in the stomach	Stomach	Contracts stomach muscle
Somatostatin	Mucosa of stomach, especially pyloric antrum; also duodenum	Presence of food in the stomach; sympathetic axon stimulation	Stomach	Restricts all gastric secretions, gastric motility, and emptying
Somatostatin	Mucosa of stomach, especially pyloric antrum; also duodenum	Presence of food in the stomach; sympathetic axon stimulation	Pancreas	Restricts pancreatic secretions
Somatostatin	Mucosa of stomach, especially pyloric antrum; also duodenum	Presence of food in the stomach; sympathetic axon stimulation	Small intestine	Reduces intestinal absorption by reducing blood flow

**Table 23.6**

## Gastric Secretion

The secretion of gastric juice is controlled by both nerves and hormones. Stimuli in the brain, stomach, and small intestine activate or inhibit gastric juice production. This is why the three phases of gastric secretion are called the cephalic, gastric, and intestinal phases (Figure 23.17). However, once gastric secretion begins, all three phases can occur simultaneously.



**Figure 23.17 The Three Phases of Gastric Secretion** Gastric secretion occurs in three phases: cephalic, gastric, and intestinal. During each phase, the secretion of gastric juice can be stimulated or inhibited.

The **cephalic phase** (reflex phase) of gastric secretion, which is relatively brief, takes place before food enters the stomach. The smell, taste, sight, or thought of food triggers this phase. For example, when you bring a piece of sushi to your lips, impulses from receptors in your taste buds or the nose are relayed to your brain, which returns signals that increase gastric secretion to prepare your stomach for digestion. This enhanced secretion is a conditioned reflex, meaning it occurs only if you like or want a particular food. Depression and loss of appetite can suppress the cephalic reflex.

The **gastric phase** of secretion lasts 3 to 4 hours, and is set in motion by local neural and hormonal mechanisms triggered by the entry of food into the stomach. For example, when your sushi reaches the stomach, it creates distention that activates the

stretch receptors. This stimulates parasympathetic neurons to release acetylcholine, which then provokes increased secretion of gastric juice. Partially digested proteins, caffeine, and rising pH stimulate the release of gastrin from enteroendocrine G cells, which in turn induces parietal cells to increase their production of HCl, which is needed to create an acidic environment for the conversion of pepsinogen to pepsin, and protein digestion. Additionally, the release of gastrin activates vigorous smooth muscle contractions. However, it should be noted that the stomach does have a natural means of avoiding excessive acid secretion and potential heartburn. Whenever pH levels drop too low, cells in the stomach react by suspending HCl secretion and increasing mucous secretions.

The **intestinal phase** of gastric secretion has both excitatory and inhibitory elements. The duodenum has a major role in regulating the stomach and its emptying. When partially digested food fills the duodenum, intestinal mucosal cells release a hormone called intestinal (enteric) gastrin, which further excites gastric juice secretion. This stimulatory activity is brief, however, because when the intestine distends with chyme, the enterogastric reflex inhibits secretion. One of the effects of this reflex is to close the pyloric sphincter, which blocks additional chyme from entering the duodenum.

## The Mucosal Barrier

The mucosa of the stomach is exposed to the highly corrosive acidity of gastric juice. Gastric enzymes that can digest protein can also digest the stomach itself. The stomach is protected from self-digestion by the **mucosal barrier**. This barrier has several components. First, the stomach wall is covered by a thick coating of bicarbonate-rich mucus. This mucus forms a physical barrier, and its bicarbonate ions neutralize acid. Second, the epithelial cells of the stomach's mucosa meet at tight junctions, which block gastric juice from penetrating the underlying tissue layers. Finally, stem cells located where gastric glands join the gastric pits quickly replace damaged epithelial mucosal cells, when the epithelial cells are shed. In fact, the surface epithelium of the stomach is completely replaced every 3 to 6 days.

# Homeostatic IMBALANCES

## Ulcers: When the Mucosal Barrier Breaks Down

As effective as the mucosal barrier is, it is not a “fail-safe” mechanism. Sometimes, gastric juice eats away at the superficial lining of the stomach mucosa, creating erosions, which mostly heal on their own. Deeper and larger erosions are called ulcers.

Why does the mucosal barrier break down? A number of factors can interfere with its ability to protect the stomach lining. The majority of all ulcers are caused by either excessive intake of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, or *Helicobacter pylori* infection.

Antacids help relieve symptoms of ulcers such as “burning” pain and indigestion. When ulcers are caused by NSAID use, switching to other classes of pain relievers allows healing. When caused by *H. pylori* infection, antibiotics are effective.

A potential complication of ulcers is perforation: Perforated ulcers create a hole in the stomach wall, resulting in peritonitis (inflammation of the peritoneum). These ulcers must be repaired surgically.

## Digestive Functions of the Stomach

The stomach participates in virtually all the digestive activities with the exception of ingestion and defecation. Although almost all absorption takes place in the small intestine, the stomach does absorb some nonpolar substances, such as alcohol and aspirin.

### Mechanical Digestion

Within a few moments after food enters your stomach, mixing waves begin to occur at intervals of approximately 20 seconds. A **mixing wave** is a unique type of peristalsis that mixes and softens the food with gastric juices to create chyme. The initial mixing waves are relatively gentle, but these are followed by more intense waves, starting at the body of the stomach and increasing in force as they reach the pylorus. It is fair to say that long before your sushi exits through the pyloric sphincter, it bears little resemblance to the sushi you ate.

The pylorus, which holds around 30 mL (1 fluid ounce) of chyme, acts as a filter, permitting only liquids and small food particles to pass through the mostly, but not fully, closed pyloric sphincter. In a process called **gastric emptying**, rhythmic mixing waves force about 3 mL of chyme at a time through the pyloric sphincter and into the duodenum. Release of a

greater amount of chyme at one time would overwhelm the capacity of the small intestine to handle it. The rest of the chyme is pushed back into the body of the stomach, where it continues mixing. This process is repeated when the next mixing waves force more chyme into the duodenum.

Gastric emptying is regulated by both the stomach and the duodenum. The presence of chyme in the duodenum activates receptors that inhibit gastric secretion. This prevents additional chyme from being released by the stomach before the duodenum is ready to process it.

### Chemical Digestion

The fundus plays an important role, because it stores both undigested food and gases that are released during the process of chemical digestion. Food may sit in the fundus of the stomach for a while before being mixed with the chyme. While the food is in the fundus, the digestive activities of salivary amylase continue until the food begins mixing with the acidic chyme. Ultimately, mixing waves incorporate this food with the chyme, the acidity of which inactivates salivary amylase and activates lingual lipase. Lingual lipase then begins breaking down triglycerides into free fatty acids, and mono- and diglycerides.

The breakdown of protein begins in the stomach through the actions of HCl and the enzyme pepsin. During infancy, gastric glands also produce rennin, an enzyme that helps digest milk protein.

Its numerous digestive functions notwithstanding, there is only one stomach function necessary to life: the production of intrinsic factor. The intestinal absorption of vitamin B<sub>12</sub>, which is necessary for both the production of mature red blood cells and normal neurological functioning, cannot occur without intrinsic factor. People who undergo total gastrectomy (stomach removal)—for life-threatening stomach cancer, for example—can survive with minimal digestive dysfunction if they receive vitamin B<sub>12</sub> injections.

The contents of the stomach are completely emptied into the duodenum within 2 to 4 hours after you eat a meal. Different types of food take different amounts of time to process. Foods heavy in carbohydrates empty fastest, followed by high-protein foods. Meals with a high triglyceride content remain in the stomach the longest. Since enzymes in the small intestine digest fats slowly, food can stay in the stomach for 6 hours or longer when the duodenum is processing fatty chyme. However, note that this is still a fraction of the 24 to 72 hours that full digestion typically takes from start to finish.

## 23.5 | The Small and Large Intestines

By the end of this section, you will be able to:

- Compare and contrast the location and gross anatomy of the small and large intestines
- Identify three main adaptations of the small intestine wall that increase its absorptive capacity
- Describe the mechanical and chemical digestion of chyme upon its release into the small intestine
- List three features unique to the wall of the large intestine and identify their contributions to its function
- Identify the beneficial roles of the bacterial flora in digestive system functioning
- Trace the pathway of food waste from its point of entry into the large intestine through its exit from the body as feces

The word intestine is derived from a Latin root meaning “internal,” and indeed, the two organs together nearly fill the interior of the abdominal cavity. In addition, called the small and large bowel, or colloquially the “guts,” they constitute the greatest mass and length of the alimentary canal and, with the exception of ingestion, perform all digestive system functions.

### The Small Intestine

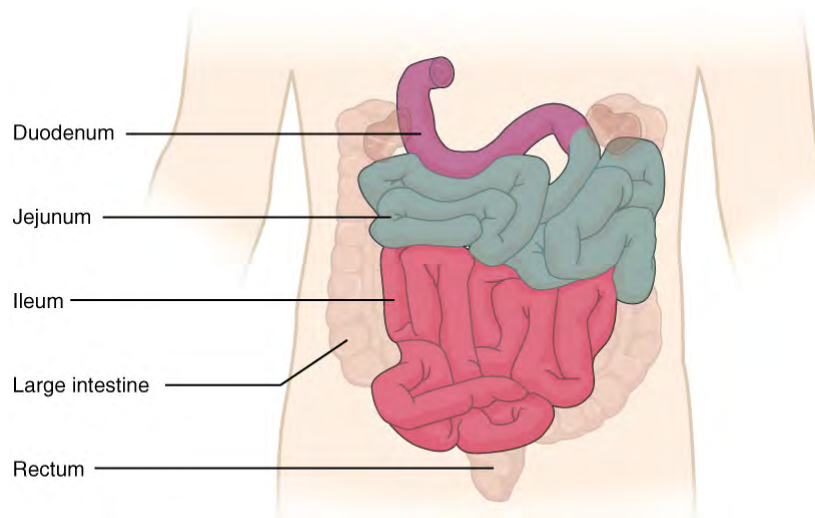
Chyme released from the stomach enters the **small intestine**, which is the primary digestive organ in the body. Not only is this where most digestion occurs, it is also where practically all absorption occurs. The longest part of the alimentary canal, the small intestine is about 3.05 meters (10 feet) long in a living person (but about twice as long in a cadaver due to the loss of muscle tone). Since this makes it about five times longer than the large intestine, you might wonder why it is called “small.” In fact, its name derives from its relatively smaller diameter of only about 2.54 cm (1 in), compared with 7.62 cm (3 in) for the large intestine. As we’ll see shortly, in addition to its length, the folds and projections of the lining of the small intestine work to give it an enormous surface area, which is approximately 200 m<sup>2</sup>, more than 100 times the surface area of your skin. This large surface area is necessary for complex processes of digestion and absorption that occur within it.

## Structure

The coiled tube of the small intestine is subdivided into three regions. From proximal (at the stomach) to distal, these are the duodenum, jejunum, and ileum (**Figure 23.18**).

The shortest region is the 25.4-cm (10-in) **duodenum**, which begins at the pyloric sphincter. Just past the pyloric sphincter, it bends posteriorly behind the peritoneum, becoming retroperitoneal, and then makes a C-shaped curve around the head of the pancreas before ascending anteriorly again to return to the peritoneal cavity and join the jejunum. The duodenum can therefore be subdivided into four segments: the superior, descending, horizontal, and ascending duodenum.

Of particular interest is the **hepatopancreatic ampulla** (ampulla of Vater). Located in the duodenal wall, the ampulla marks the transition from the anterior portion of the alimentary canal to the mid-region, and is where the bile duct (through which bile passes from the liver) and the **main pancreatic duct** (through which pancreatic juice passes from the pancreas) join. This ampulla opens into the duodenum at a tiny volcano-shaped structure called the **major duodenal papilla**. The **hepatopancreatic sphincter** (sphincter of Oddi) regulates the flow of both bile and pancreatic juice from the ampulla into the duodenum.



**Figure 23.18 Small Intestine** The three regions of the small intestine are the duodenum, jejunum, and ileum.

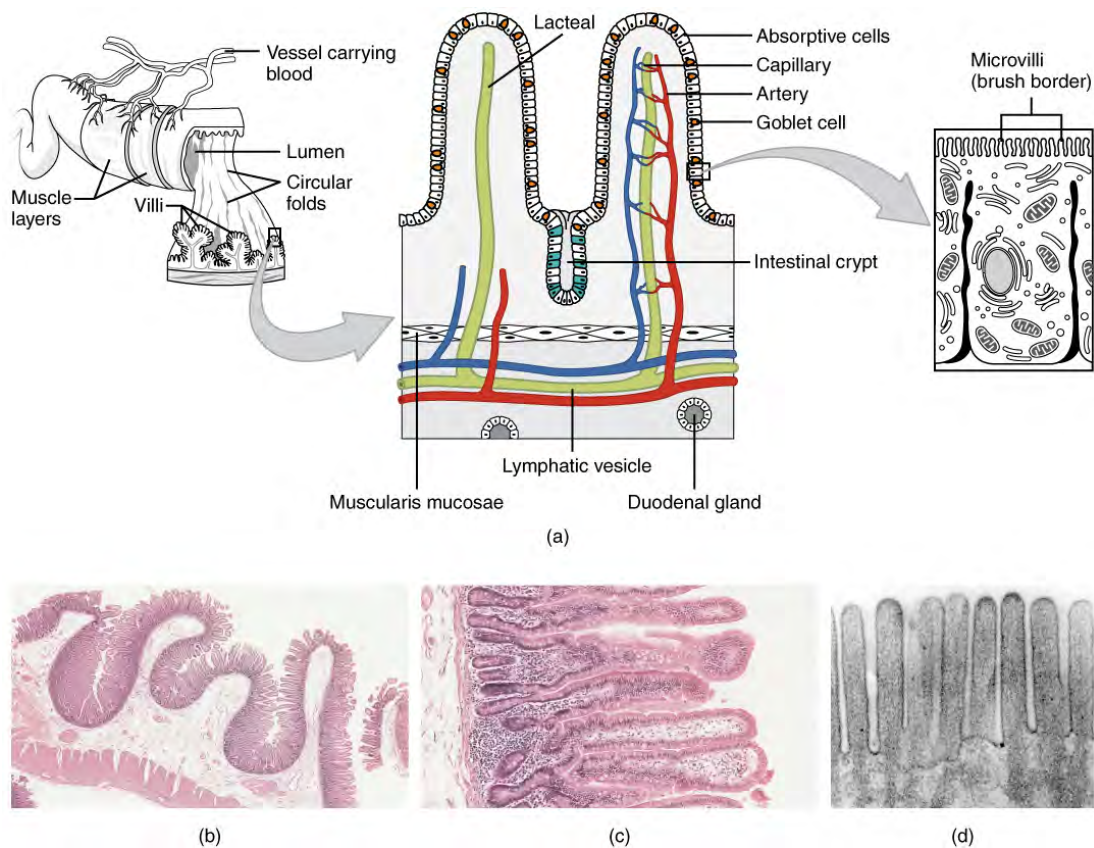
The **jejunum** is about 0.9 meters (3 feet) long (in life) and runs from the duodenum to the ileum. Jejunum means “empty” in Latin and supposedly was so named by the ancient Greeks who noticed it was always empty at death. No clear demarcation exists between the jejunum and the final segment of the small intestine, the ileum.

The **ileum** is the longest part of the small intestine, measuring about 1.8 meters (6 feet) in length. It is thicker, more vascular, and has more developed mucosal folds than the jejunum. The ileum joins the cecum, the first portion of the large intestine, at the **ileocecal sphincter** (or valve). The jejunum and ileum are tethered to the posterior abdominal wall by the mesentery. The large intestine frames these three parts of the small intestine.

Parasympathetic nerve fibers from the vagus nerve and sympathetic nerve fibers from the thoracic splanchnic nerve provide extrinsic innervation to the small intestine. The superior mesenteric artery is its main arterial supply. Veins run parallel to the arteries and drain into the superior mesenteric vein. Nutrient-rich blood from the small intestine is then carried to the liver via the hepatic portal vein.

## Histology

The wall of the small intestine is composed of the same four layers typically present in the alimentary system. However, three features of the mucosa and submucosa are unique. These features, which increase the absorptive surface area of the small intestine more than 600-fold, include circular folds, villi, and microvilli (**Figure 23.19**). These adaptations are most abundant in the proximal two-thirds of the small intestine, where the majority of absorption occurs.



**Figure 23.19 Histology of the Small Intestine** (a) The absorptive surface of the small intestine is vastly enlarged by the presence of circular folds, villi, and microvilli. (b) Micrograph of the circular folds. (c) Micrograph of the villi. (d) Electron micrograph of the microvilli. From left to right, LM x 56, LM x 508, EM x 196,000. (credit b-d: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

### Circular folds

Also called a plica circulaire, a **circular fold** is a deep ridge in the mucosa and submucosa. Beginning near the proximal part of the duodenum and ending near the middle of the ileum, these folds facilitate absorption. Their shape causes the chyme to spiral, rather than move in a straight line, through the small intestine. Spiraling slows the movement of chyme and provides the time needed for nutrients to be fully absorbed.

### Villi

Within the circular folds are small (0.5–1 mm long) hairlike vascularized projections called **villi** (singular = villus) that give the mucosa a furry texture. There are about 20 to 40 villi per square millimeter, increasing the surface area of the epithelium tremendously. The mucosal epithelium, primarily composed of absorptive cells, covers the villi. In addition to muscle and connective tissue to support its structure, each villus contains a capillary bed composed of one arteriole and one venule, as well as a lymphatic capillary called a **lacteal**. The breakdown products of carbohydrates and proteins (sugars and amino acids) can enter the bloodstream directly, but lipid breakdown products are absorbed by the lacteals and transported to the bloodstream via the lymphatic system.

### Microvilli

As their name suggests, **microvilli** (singular = microvillus) are much smaller (1  $\mu\text{m}$ ) than villi. They are cylindrical apical surface extensions of the plasma membrane of the mucosa's epithelial cells, and are supported by microfilaments within those cells. Although their small size makes it difficult to see each microvillus, their combined microscopic appearance suggests a mass of bristles, which is termed the **brush border**. Fixed to the surface of the microvilli membranes are enzymes that finish digesting carbohydrates and proteins. There are an estimated 200 million microvilli per square millimeter of small intestine, greatly expanding the surface area of the plasma membrane and thus greatly enhancing absorption.

## Intestinal Glands

In addition to the three specialized absorptive features just discussed, the mucosa between the villi is dotted with deep crevices that each lead into a tubular **intestinal gland** (crypt of Lieberkühn), which is formed by cells that line the crevices (see **Figure 23.19**). These produce **intestinal juice**, a slightly alkaline (pH 7.4 to 7.8) mixture of water and mucus. Each day, about 0.95 to 1.9 liters (1 to 2 quarts) are secreted in response to the distention of the small intestine or the irritating effects of chyme on the intestinal mucosa.

The submucosa of the duodenum is the only site of the complex mucus-secreting **duodenal glands** (Brunner's glands), which produce a bicarbonate-rich alkaline mucus that buffers the acidic chyme as it enters from the stomach.

The roles of the cells in the small intestinal mucosa are detailed in **Table 23.7**.

### Cells of the Small Intestinal Mucosa

Cell type	Location in the mucosa	Function
Absorptive	Epithelium/intestinal glands	Digestion and absorption of nutrients in chyme
Goblet	Epithelium/intestinal glands	Secretion of mucus
Paneth	Intestinal glands	Secretion of the bactericidal enzyme lysozyme; phagocytosis
G cells	Intestinal glands of duodenum	Secretion of the hormone intestinal gastrin
I cells	Intestinal glands of duodenum	Secretion of the hormone cholecystokinin, which stimulates release of pancreatic juices and bile
K cells	Intestinal glands	Secretion of the hormone glucose-dependent insulinotropic peptide, which stimulates the release of insulin
M cells	Intestinal glands of duodenum and jejunum	Secretion of the hormone motilin, which accelerates gastric emptying, stimulates intestinal peristalsis, and stimulates the production of pepsin
S cells	Intestinal glands	Secretion of the hormone secretin

**Table 23.7**

## Intestinal MALT

The lamina propria of the small intestine mucosa is studded with quite a bit of MALT. In addition to solitary lymphatic nodules, aggregations of intestinal MALT, which are typically referred to as Peyer's patches, are concentrated in the distal ileum, and serve to keep bacteria from entering the bloodstream. Peyer's patches are most prominent in young people and become less distinct as you age, which coincides with the general activity of our immune system.

## Interactive LINK

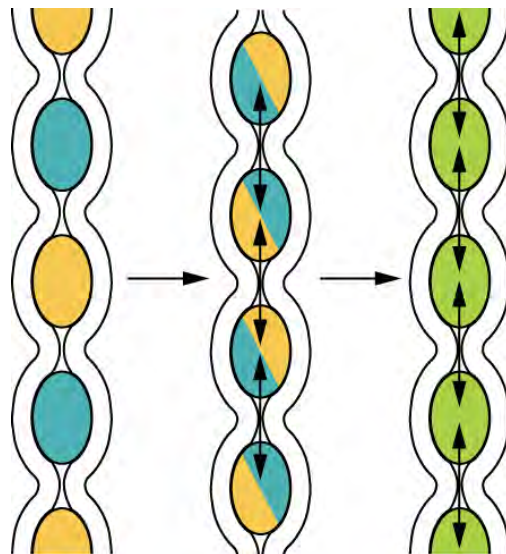


Watch this [animation \(http://openstaxcollege.org/l/sintestine\)](http://openstaxcollege.org/l/sintestine) that depicts the structure of the small intestine, and, in particular, the villi. Epithelial cells continue the digestion and absorption of nutrients and transport these nutrients to the lymphatic and circulatory systems. In the small intestine, the products of food digestion are absorbed by different structures in the villi. Which structure absorbs and transports fats?

### Mechanical Digestion in the Small Intestine

The movement of intestinal smooth muscles includes both segmentation and a form of peristalsis called migrating motility complexes. The kind of peristaltic mixing waves seen in the stomach are not observed here.

If you could see into the small intestine when it was going through segmentation, it would look as if the contents were being shoved incrementally back and forth, as the rings of smooth muscle repeatedly contract and then relax. Segmentation in the small intestine does not force chyme through the tract. Instead, it combines the chyme with digestive juices and pushes food particles against the mucosa to be absorbed. The duodenum is where the most rapid segmentation occurs, at a rate of about 12 times per minute. In the ileum, segmentations are only about eight times per minute ([Figure 23.20](#)).



**Figure 23.20 Segmentation** Segmentation separates chyme and then pushes it back together, mixing it and providing time for digestion and absorption.

When most of the chyme has been absorbed, the small intestinal wall becomes less distended. At this point, the localized segmentation process is replaced by transport movements. The duodenal mucosa secretes the hormone **motilin**, which initiates peristalsis in the form of a **migrating motility complex**. These complexes, which begin in the duodenum, force chyme through a short section of the small intestine and then stop. The next contraction begins a little bit farther down than the first, forces chyme a bit farther through the small intestine, then stops. These complexes move slowly down the small intestine, forcing chyme on the way, taking around 90 to 120 minutes to finally reach the end of the ileum. At this point, the process is repeated, starting in the duodenum.

The ileocecal valve, a sphincter, is usually in a constricted state, but when motility in the ileum increases, this sphincter

relaxes, allowing food residue to enter the first portion of the large intestine, the cecum. Relaxation of the ileocecal sphincter is controlled by both nerves and hormones. First, digestive activity in the stomach provokes the **gastroileal reflex**, which increases the force of ileal segmentation. Second, the stomach releases the hormone gastrin, which enhances ileal motility, thus relaxing the ileocecal sphincter. After chyme passes through, backward pressure helps close the sphincter, preventing backflow into the ileum. Because of this reflex, your lunch is completely emptied from your stomach and small intestine by the time you eat your dinner. It takes about 3 to 5 hours for all chyme to leave the small intestine.

### Chemical Digestion in the Small Intestine

The digestion of proteins and carbohydrates, which partially occurs in the stomach, is completed in the small intestine with the aid of intestinal and pancreatic juices. Lipids arrive in the intestine largely undigested, so much of the focus here is on lipid digestion, which is facilitated by bile and the enzyme pancreatic lipase.

Moreover, intestinal juice combines with pancreatic juice to provide a liquid medium that facilitates absorption. The intestine is also where most water is absorbed, via osmosis. The small intestine's absorptive cells also synthesize digestive enzymes and then place them in the plasma membranes of the microvilli. This distinguishes the small intestine from the stomach; that is, enzymatic digestion occurs not only in the lumen, but also on the luminal surfaces of the mucosal cells.

For optimal chemical digestion, chyme must be delivered from the stomach slowly and in small amounts. This is because chyme from the stomach is typically hypertonic, and if large quantities were forced all at once into the small intestine, the resulting osmotic water loss from the blood into the intestinal lumen would result in potentially life-threatening low blood volume. In addition, continued digestion requires an upward adjustment of the low pH of stomach chyme, along with rigorous mixing of the chyme with bile and pancreatic juices. Both processes take time, so the pumping action of the pylorus must be carefully controlled to prevent the duodenum from being overwhelmed with chyme.

## Disorders OF THE...

### Small Intestine: Lactose Intolerance

Lactose intolerance is a condition characterized by indigestion caused by dairy products. It occurs when the absorptive cells of the small intestine do not produce enough lactase, the enzyme that digests the milk sugar lactose. In most mammals, lactose intolerance increases with age. In contrast, some human populations, most notably Caucasians, are able to maintain the ability to produce lactase as adults.

In people with lactose intolerance, the lactose in chyme is not digested. Bacteria in the large intestine ferment the undigested lactose, a process that produces gas. In addition to gas, symptoms include abdominal cramps, bloating, and diarrhea. Symptom severity ranges from mild discomfort to severe pain; however, symptoms resolve once the lactose is eliminated in feces.

The hydrogen breath test is used to help diagnose lactose intolerance. Lactose-tolerant people have very little hydrogen in their breath. Those with lactose intolerance exhale hydrogen, which is one of the gases produced by the bacterial fermentation of lactose in the colon. After the hydrogen is absorbed from the intestine, it is transported through blood vessels into the lungs. There are a number of lactose-free dairy products available in grocery stores. In addition, dietary supplements are available. Taken with food, they provide lactase to help digest lactose.

## The Large Intestine

The **large intestine** is the terminal part of the alimentary canal. The primary function of this organ is to finish absorption of nutrients and water, synthesize certain vitamins, form feces, and eliminate feces from the body.

### Structure

The large intestine runs from the appendix to the anus. It frames the small intestine on three sides. Despite its being about one-half as long as the small intestine, it is called large because it is more than twice the diameter of the small intestine, about 3 inches.

### Subdivisions

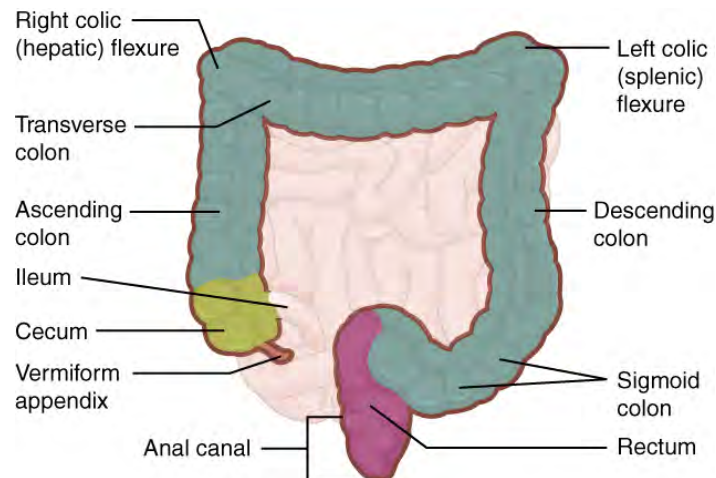
The large intestine is subdivided into four main regions: the cecum, the colon, the rectum, and the anus. The ileocecal valve, located at the opening between the ileum and the large intestine, controls the flow of chyme from the small intestine to the large intestine.

## Cecum

The first part of the large intestine is the **cecum**, a sac-like structure that is suspended inferior to the ileocecal valve. It is about 6 cm (2.4 in) long, receives the contents of the ileum, and continues the absorption of water and salts. The **appendix** (or vermiform appendix) is a winding tube that attaches to the cecum. Although the 7.6-cm (3-in) long appendix contains lymphoid tissue, suggesting an immunologic function, this organ is generally considered vestigial. However, at least one recent report postulates a survival advantage conferred by the appendix: In diarrheal illness, the appendix may serve as a bacterial reservoir to repopulate the enteric bacteria for those surviving the initial phases of the illness. Moreover, its twisted anatomy provides a haven for the accumulation and multiplication of enteric bacteria. The **mesoappendix**, the mesentery of the appendix, tethers it to the mesentery of the ileum.

## Colon

The cecum blends seamlessly with the **colon**. Upon entering the colon, the food residue first travels up the **ascending colon** on the right side of the abdomen. At the inferior surface of the liver, the colon bends to form the **right colic flexure** (hepatic flexure) and becomes the **transverse colon**. The region defined as hindgut begins with the last third of the transverse colon and continues on. Food residue passing through the transverse colon travels across to the left side of the abdomen, where the colon angles sharply immediately inferior to the spleen, at the **left colic flexure** (splenic flexure). From there, food residue passes through the **descending colon**, which runs down the left side of the posterior abdominal wall. After entering the pelvis inferiorly, it becomes the s-shaped **sigmoid colon**, which extends medially to the midline (**Figure 23.21**). The ascending and descending colon, and the rectum (discussed next) are located in the retroperitoneum. The transverse and sigmoid colon are tethered to the posterior abdominal wall by the mesocolon.



**Figure 23.21 Large Intestine** The large intestine includes the cecum, colon, and rectum.

# Homeostatic IMBALANCES

## Colorectal Cancer

Each year, approximately 140,000 Americans are diagnosed with colorectal cancer, and another 49,000 die from it, making it one of the most deadly malignancies. People with a family history of colorectal cancer are at increased risk. Smoking, excessive alcohol consumption, and a diet high in animal fat and protein also increase the risk. Despite popular opinion to the contrary, studies support the conclusion that dietary fiber and calcium do not reduce the risk of colorectal cancer.

Colorectal cancer may be signaled by constipation or diarrhea, cramping, abdominal pain, and rectal bleeding. Bleeding from the rectum may be either obvious or occult (hidden in feces). Since most colon cancers arise from benign mucosal growths called polyps, cancer prevention is focused on identifying these polyps. The colonoscopy is both diagnostic and therapeutic. Colonoscopy not only allows identification of precancerous polyps, the procedure also enables them to be removed before they become malignant. Screening for fecal occult blood tests and colonoscopy is recommended for those over 50 years of age.

## Rectum

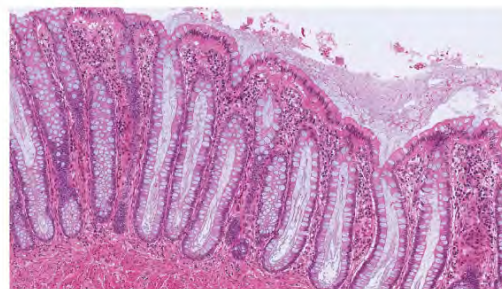
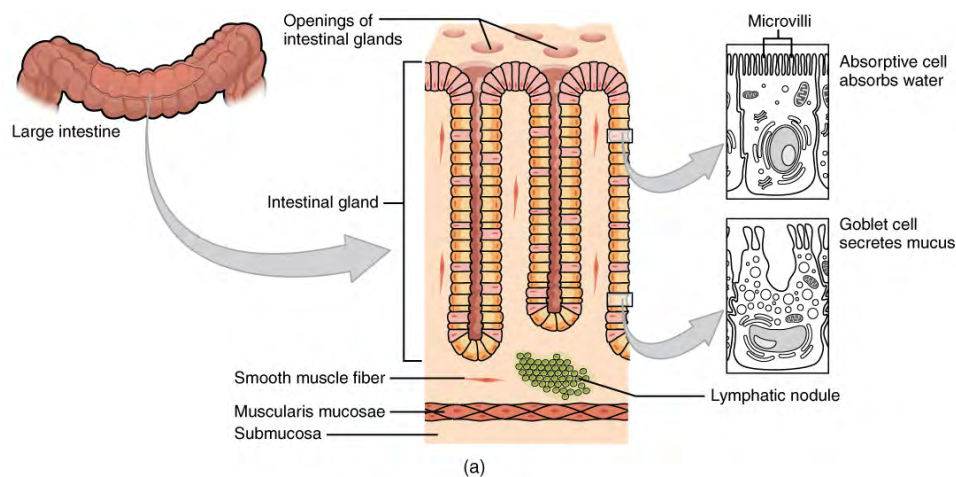
Food residue leaving the sigmoid colon enters the **rectum** in the pelvis, near the third sacral vertebra. The final 20.3 cm (8 in) of the alimentary canal, the rectum extends anterior to the sacrum and coccyx. Even though rectum is Latin for “straight,” this structure follows the curved contour of the sacrum and has three lateral bends that create a trio of internal transverse folds called the **rectal valves**. These valves help separate the feces from gas to prevent the simultaneous passage of feces and gas.

## Anal Canal

Finally, food residue reaches the last part of the large intestine, the **anal canal**, which is located in the perineum, completely outside of the abdominopelvic cavity. This 3.8–5 cm (1.5–2 in) long structure opens to the exterior of the body at the anus. The anal canal includes two sphincters. The **internal anal sphincter** is made of smooth muscle, and its contractions are involuntary. The **external anal sphincter** is made of skeletal muscle, which is under voluntary control. Except when defecating, both usually remain closed.

## Histology

There are several notable differences between the walls of the large and small intestines (**Figure 23.22**). For example, few enzyme-secreting cells are found in the wall of the large intestine, and there are no circular folds or villi. Other than in the anal canal, the mucosa of the colon is simple columnar epithelium made mostly of enterocytes (absorptive cells) and goblet cells. In addition, the wall of the large intestine has far more intestinal glands, which contain a vast population of enterocytes and goblet cells. These goblet cells secrete mucus that eases the movement of feces and protects the intestine from the effects of the acids and gases produced by enteric bacteria. The enterocytes absorb water and salts as well as vitamins produced by your intestinal bacteria.

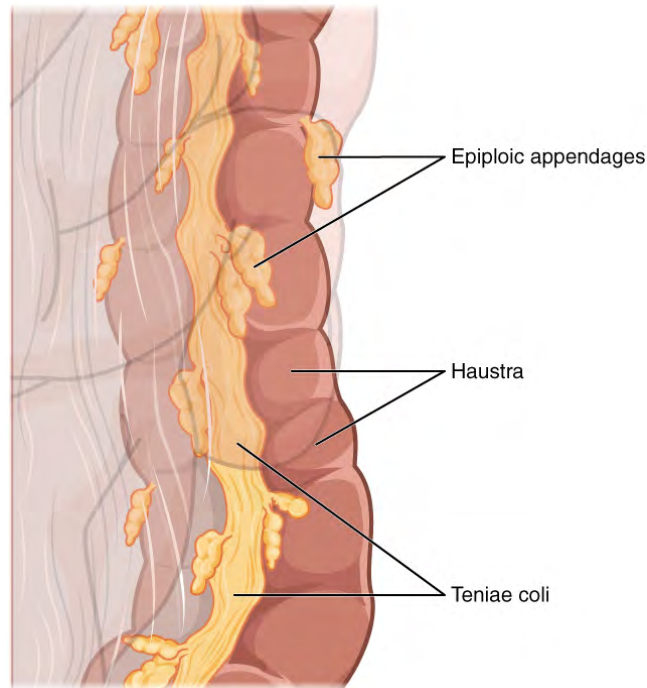


**Figure 23.22 Histology of the large Intestine** (a) The histologies of the large intestine and small intestine (not shown) are adapted for the digestive functions of each organ. (b) This micrograph shows the colon's simple columnar epithelium and goblet cells. LM x 464. (credit b: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

## Anatomy

Three features are unique to the large intestine: teniae coli, haustra, and epiploic appendages (**Figure 23.23**). The **teniae coli**

are three bands of smooth muscle that make up the longitudinal muscle layer of the muscularis of the large intestine, except at its terminal end. Tonic contractions of the teniae coli bunch up the colon into a succession of pouches called **haustra** (singular = haustrum), which are responsible for the wrinkled appearance of the colon. Attached to the teniae coli are small, fat-filled sacs of visceral peritoneum called **epiploic appendages**. The purpose of these is unknown. Although the rectum and anal canal have neither teniae coli nor haustra, they do have well-developed layers of muscularis that create the strong contractions needed for defecation.



**Figure 23.23 Teniae Coli, Haustra, and Epiploic Appendages**

The stratified squamous epithelial mucosa of the anal canal connects to the skin on the outside of the anus. This mucosa varies considerably from that of the rest of the colon to accommodate the high level of abrasion as feces pass through. The anal canal's mucous membrane is organized into longitudinal folds, each called an **anal column**, which house a grid of arteries and veins. Two superficial venous plexuses are found in the anal canal: one within the anal columns and one at the anus.

Depressions between the anal columns, each called an **anal sinus**, secrete mucus that facilitates defecation. The **pectinate line** (or dentate line) is a horizontal, jagged band that runs circumferentially just below the level of the anal sinuses, and represents the junction between the hindgut and external skin. The mucosa above this line is fairly insensitive, whereas the area below is very sensitive. The resulting difference in pain threshold is due to the fact that the upper region is innervated by visceral sensory fibers, and the lower region is innervated by somatic sensory fibers.

### Bacterial Flora

Most bacteria that enter the alimentary canal are killed by lysozyme, defensins, HCl, or protein-digesting enzymes. However, trillions of bacteria live within the large intestine and are referred to as the **bacterial flora**. Most of the more than 700 species of these bacteria are nonpathogenic commensal organisms that cause no harm as long as they stay in the gut lumen. In fact, many facilitate chemical digestion and absorption, and some synthesize certain vitamins, mainly biotin, pantothenic acid, and vitamin K. Some are linked to increased immune response. A refined system prevents these bacteria from crossing the mucosal barrier. First, peptidoglycan, a component of bacterial cell walls, activates the release of chemicals by the mucosa's epithelial cells, which draft immune cells, especially dendritic cells, into the mucosa. Dendritic cells open the tight junctions between epithelial cells and extend probes into the lumen to evaluate the microbial antigens. The dendritic cells with antigens then travel to neighboring lymphoid follicles in the mucosa where T cells inspect for antigens. This process triggers an IgA-mediated response, if warranted, in the lumen that blocks the commensal organisms from infiltrating the mucosa and setting off a far greater, widespread systematic reaction.

## Digestive Functions of the Large Intestine

The residue of chyme that enters the large intestine contains few nutrients except water, which is reabsorbed as the residue lingers in the large intestine, typically for 12 to 24 hours. Thus, it may not surprise you that the large intestine can be completely removed without significantly affecting digestive functioning. For example, in severe cases of inflammatory bowel disease, the large intestine can be removed by a procedure known as a colectomy. Often, a new fecal pouch can be crafted from the small intestine and sutured to the anus, but if not, an ileostomy can be created by bringing the distal ileum through the abdominal wall, allowing the watery chyme to be collected in a bag-like adhesive appliance.

### Mechanical Digestion

In the large intestine, mechanical digestion begins when chyme moves from the ileum into the cecum, an activity regulated by the ileocecal sphincter. Right after you eat, peristalsis in the ileum forces chyme into the cecum. When the cecum is distended with chyme, contractions of the ileocecal sphincter strengthen. Once chyme enters the cecum, colon movements begin.

Mechanical digestion in the large intestine includes a combination of three types of movements. The presence of food residues in the colon stimulates a slow-moving **haustral contraction**. This type of movement involves sluggish segmentation, primarily in the transverse and descending colons. When a haustrum is distended with chyme, its muscle contracts, pushing the residue into the next haustrum. These contractions occur about every 30 minutes, and each last about 1 minute. These movements also mix the food residue, which helps the large intestine absorb water. The second type of movement is peristalsis, which, in the large intestine, is slower than in the more proximal portions of the alimentary canal. The third type is a **mass movement**. These strong waves start midway through the transverse colon and quickly force the contents toward the rectum. Mass movements usually occur three or four times per day, either while you eat or immediately afterward. Distension in the stomach and the breakdown products of digestion in the small intestine provoke the **gastrocolic reflex**, which increases motility, including mass movements, in the colon. Fiber in the diet both softens the stool and increases the power of colonic contractions, optimizing the activities of the colon.

### Chemical Digestion

Although the glands of the large intestine secrete mucus, they do not secrete digestive enzymes. Therefore, chemical digestion in the large intestine occurs exclusively because of bacteria in the lumen of the colon. Through the process of **saccharolytic fermentation**, bacteria break down some of the remaining carbohydrates. This results in the discharge of hydrogen, carbon dioxide, and methane gases that create **flatus** (gas) in the colon; flatulence is excessive flatus. Each day, up to 1500 mL of flatus is produced in the colon. More is produced when you eat foods such as beans, which are rich in otherwise indigestible sugars and complex carbohydrates like soluble dietary fiber.

### Absorption, Feces Formation, and Defecation

The small intestine absorbs about 90 percent of the water you ingest (either as liquid or within solid food). The large intestine absorbs most of the remaining water, a process that converts the liquid chyme residue into semisolid **feces** (“stool”). Feces is composed of undigested food residues, unabsorbed digested substances, millions of bacteria, old epithelial cells from the GI mucosa, inorganic salts, and enough water to let it pass smoothly out of the body. Of every 500 mL (17 ounces) of food residue that enters the cecum each day, about 150 mL (5 ounces) become feces.

Feces are eliminated through contractions of the rectal muscles. You help this process by a voluntary procedure called **Valsalva’s maneuver**, in which you increase intra-abdominal pressure by contracting your diaphragm and abdominal wall muscles, and closing your glottis.

The process of defecation begins when mass movements force feces from the colon into the rectum, stretching the rectal wall and provoking the defecation reflex, which eliminates feces from the rectum. This parasympathetic reflex is mediated by the spinal cord. It contracts the sigmoid colon and rectum, relaxes the internal anal sphincter, and initially contracts the external anal sphincter. The presence of feces in the anal canal sends a signal to the brain, which gives you the choice of voluntarily opening the external anal sphincter (defecating) or keeping it temporarily closed. If you decide to delay defecation, it takes a few seconds for the reflex contractions to stop and the rectal walls to relax. The next mass movement will trigger additional defecation reflexes until you defecate.

If defecation is delayed for an extended time, additional water is absorbed, making the feces firmer and potentially leading to constipation. On the other hand, if the waste matter moves too quickly through the intestines, not enough water is absorbed, and diarrhea can result. This can be caused by the ingestion of foodborne pathogens. In general, diet, health, and stress determine the frequency of bowel movements. The number of bowel movements varies greatly between individuals, ranging from two or three per day to three or four per week.

## Interactive LINK



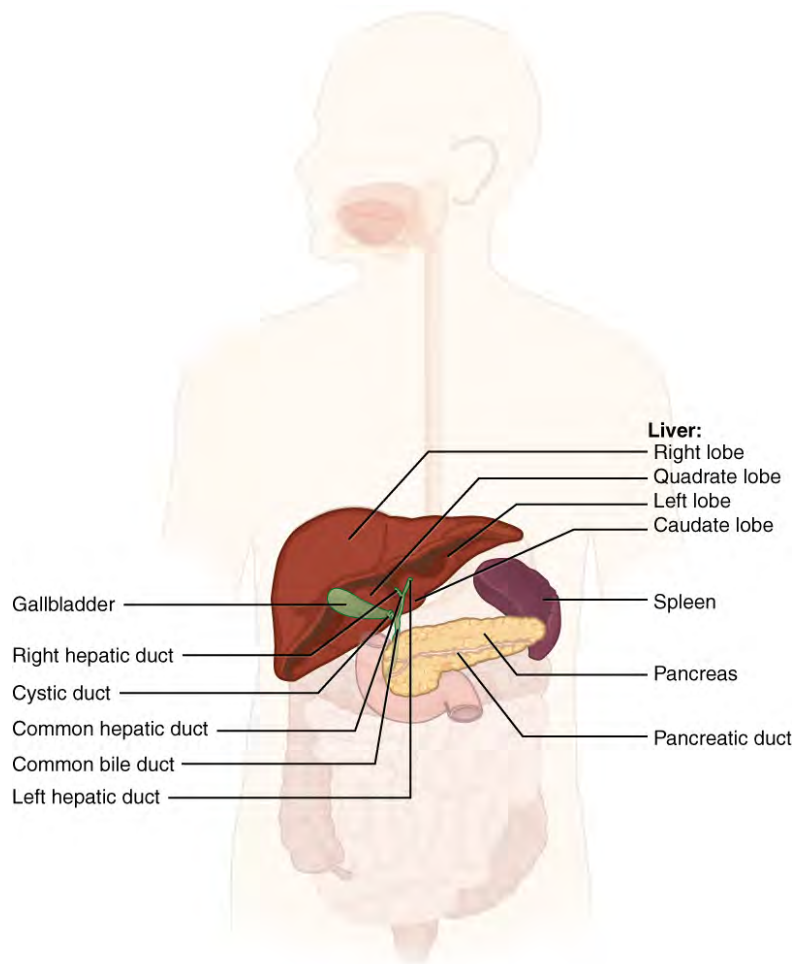
By watching this **animation** (<http://openstaxcollege.org/l/foodgroups>) you will see that for the various food groups—proteins, fats, and carbohydrates—digestion begins in different parts of the digestion system, though all end in the same place. Of the three major food classes (carbohydrates, fats, and proteins), which is digested in the mouth, the stomach, and the small intestine?

## 23.6 | Accessory Organs in Digestion: The Liver, Pancreas, and Gallbladder

By the end of this section, you will be able to:

- State the main digestive roles of the liver, pancreas, and gallbladder
- Identify three main features of liver histology that are critical to its function
- Discuss the composition and function of bile
- Identify the major types of enzymes and buffers present in pancreatic juice

Chemical digestion in the small intestine relies on the activities of three accessory digestive organs: the liver, pancreas, and gallbladder (**Figure 23.24**). The digestive role of the liver is to produce bile and export it to the duodenum. The gallbladder primarily stores, concentrates, and releases bile. The pancreas produces pancreatic juice, which contains digestive enzymes and bicarbonate ions, and delivers it to the duodenum.



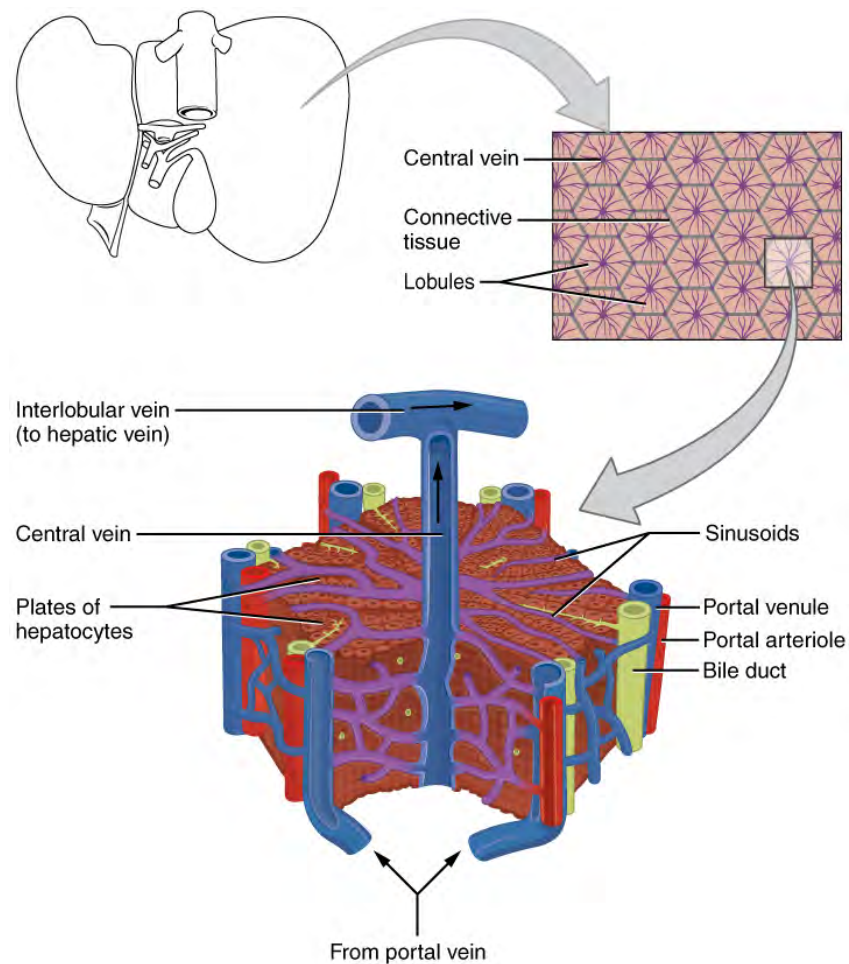
**Figure 23.24 Accessory Organs** The liver, pancreas, and gallbladder are considered accessory digestive organs, but their roles in the digestive system are vital.

## The Liver

The **liver** is the largest gland in the body, weighing about three pounds in an adult. It is also one of the most important organs. In addition to being an accessory digestive organ, it plays a number of roles in metabolism and regulation. The liver lies inferior to the diaphragm in the right upper quadrant of the abdominal cavity and receives protection from the surrounding ribs.

The liver is divided into two primary lobes: a large right lobe and a much smaller left lobe. In the right lobe, some anatomists also identify an inferior quadrate lobe and a posterior caudate lobe, which are defined by internal features. The liver is connected to the abdominal wall and diaphragm by five peritoneal folds referred to as ligaments. These are the falciform ligament, the coronary ligament, two lateral ligaments, and the ligamentum teres hepatis. The falciform ligament and ligamentum teres hepatis are actually remnants of the umbilical vein, and separate the right and left lobes anteriorly. The lesser omentum tethers the liver to the lesser curvature of the stomach.

The **porta hepatis** (“gate to the liver”) is where the **hepatic artery** and **hepatic portal vein** enter the liver. These two vessels, along with the common hepatic duct, run behind the lateral border of the lesser omentum on the way to their destinations. As shown in **Figure 23.25**, the hepatic artery delivers oxygenated blood from the heart to the liver. The hepatic portal vein delivers partially deoxygenated blood containing nutrients absorbed from the small intestine and actually supplies more oxygen to the liver than do the much smaller hepatic arteries. In addition to nutrients, drugs and toxins are also absorbed. After processing the bloodborne nutrients and toxins, the liver releases nutrients needed by other cells back into the blood, which drains into the central vein and then through the hepatic vein to the inferior vena cava. With this hepatic portal circulation, all blood from the alimentary canal passes through the liver. This largely explains why the liver is the most common site for the metastasis of cancers that originate in the alimentary canal.



**Figure 23.25 Microscopic Anatomy of the Liver** The liver receives oxygenated blood from the hepatic artery and nutrient-rich deoxygenated blood from the hepatic portal vein.

### Histology

The liver has three main components: hepatocytes, bile canaliculi, and hepatic sinusoids. A **hepatocyte** is the liver's main cell type, accounting for around 80 percent of the liver's volume. These cells play a role in a wide variety of secretory, metabolic, and endocrine functions. Plates of hepatocytes called hepatic laminae radiate outward from the portal vein in each **hepatic lobule**.

Between adjacent hepatocytes, grooves in the cell membranes provide room for each **bile canaliculus** (plural = canaliculi). These small ducts accumulate the bile produced by hepatocytes. From here, bile flows first into bile ductules and then into bile ducts. The bile ducts unite to form the larger right and left hepatic ducts, which themselves merge and exit the liver as the **common hepatic duct**. This duct then joins with the cystic duct from the gallbladder, forming the **common bile duct** through which bile flows into the small intestine.

A **hepatic sinusoid** is an open, porous blood space formed by fenestrated capillaries from nutrient-rich hepatic portal veins and oxygen-rich hepatic arteries. Hepatocytes are tightly packed around the fenestrated endothelium of these spaces, giving them easy access to the blood. From their central position, hepatocytes process the nutrients, toxins, and waste materials carried by the blood. Materials such as bilirubin are processed and excreted into the bile canaliculi. Other materials including proteins, lipids, and carbohydrates are processed and secreted into the sinusoids or just stored in the cells until called upon. The hepatic sinusoids combine and send blood to a **central vein**. Blood then flows through a **hepatic vein** into the inferior vena cava. This means that blood and bile flow in opposite directions. The hepatic sinusoids also contain star-shaped **reticuloendothelial cells** (Kupffer cells), phagocytes that remove dead red and white blood cells, bacteria, and other foreign material that enter the sinusoids. The **portal triad** is a distinctive arrangement around the perimeter of hepatic lobules, consisting of three basic structures: a bile duct, a hepatic artery branch, and a hepatic portal vein branch.

## Bile

Recall that lipids are hydrophobic, that is, they do not dissolve in water. Thus, before they can be digested in the watery environment of the small intestine, large lipid globules must be broken down into smaller lipid globules, a process called emulsification. **Bile** is a mixture secreted by the liver to accomplish the emulsification of lipids in the small intestine.

Hepatocytes secrete about one liter of bile each day. A yellow-brown or yellow-green alkaline solution (pH 7.6 to 8.6), bile is a mixture of water, bile salts, bile pigments, phospholipids (such as lecithin), electrolytes, cholesterol, and triglycerides. The components most critical to emulsification are bile salts and phospholipids, which have a nonpolar (hydrophobic) region as well as a polar (hydrophilic) region. The hydrophobic region interacts with the large lipid molecules, whereas the hydrophilic region interacts with the watery chyme in the intestine. This results in the large lipid globules being pulled apart into many tiny lipid fragments of about 1  $\mu\text{m}$  in diameter. This change dramatically increases the surface area available for lipid-digesting enzyme activity. This is the same way dish soap works on fats mixed with water.

Bile salts act as emulsifying agents, so they are also important for the absorption of digested lipids. While most constituents of bile are eliminated in feces, bile salts are reclaimed by the **enterohepatic circulation**. Once bile salts reach the ileum, they are absorbed and returned to the liver in the hepatic portal blood. The hepatocytes then excrete the bile salts into newly formed bile. Thus, this precious resource is recycled.

**Bilirubin**, the main bile pigment, is a waste product produced when the spleen removes old or damaged red blood cells from the circulation. These breakdown products, including proteins, iron, and toxic bilirubin, are transported to the liver via the splenic vein of the hepatic portal system. In the liver, proteins and iron are recycled, whereas bilirubin is excreted in the bile. It accounts for the green color of bile. Bilirubin is eventually transformed by intestinal bacteria into stercobilin, a brown pigment that gives your stool its characteristic color! In some disease states, bile does not enter the intestine, resulting in white ('acholic') stool with a high fat content, since virtually no fats are broken down or absorbed.

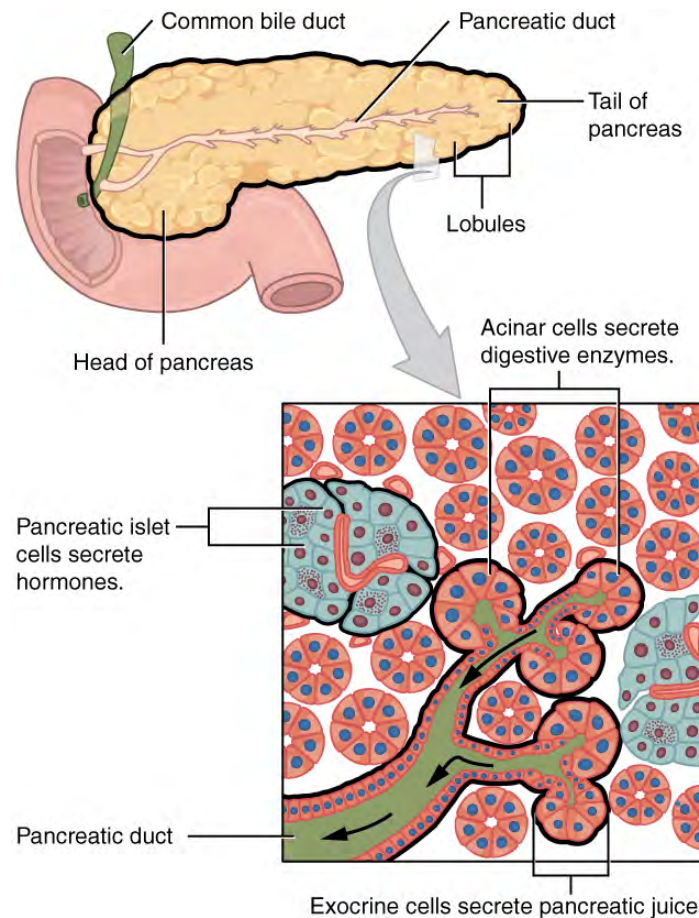
Hepatocytes work non-stop, but bile production increases when fatty chyme enters the duodenum and stimulates the secretion of the gut hormone secretin. Between meals, bile is produced but conserved. The valve-like hepatopancreatic ampulla closes, allowing bile to divert to the gallbladder, where it is concentrated and stored until the next meal.



Watch this **video** (<http://openstaxcollege.org/l/liver>) to see the structure of the liver and how this structure supports the functions of the liver, including the processing of nutrients, toxins, and wastes. At rest, about 1500 mL of blood per minute flow through the liver. What percentage of this blood flow comes from the hepatic portal system?

## The Pancreas

The soft, oblong, glandular **pancreas** lies transversely in the retroperitoneum behind the stomach. Its head is nestled into the “c-shaped” curvature of the duodenum with the body extending to the left about 15.2 cm (6 in) and ending as a tapering tail in the hilum of the spleen. It is a curious mix of exocrine (secreting digestive enzymes) and endocrine (releasing hormones into the blood) functions (**Figure 23.26**).



**Figure 23.26 Exocrine and Endocrine Pancreas** The pancreas has a head, a body, and a tail. It delivers pancreatic juice to the duodenum through the pancreatic duct.

The exocrine part of the pancreas arises as little grape-like cell clusters, each called an **acinus** (plural = acini), located at the terminal ends of pancreatic ducts. These acinar cells secrete enzyme-rich **pancreatic juice** into tiny merging ducts that form two dominant ducts. The larger duct fuses with the common bile duct (carrying bile from the liver and gallbladder) just before entering the duodenum via a common opening (the hepatopancreatic ampulla). The smooth muscle sphincter of the hepatopancreatic ampulla controls the release of pancreatic juice and bile into the small intestine. The second and smaller pancreatic duct, the **accessory duct** (duct of Santorini), runs from the pancreas directly into the duodenum, approximately 1 inch above the hepatopancreatic ampulla. When present, it is a persistent remnant of pancreatic development.

Scattered through the sea of exocrine acini are small islands of endocrine cells, the islets of Langerhans. These vital cells produce the hormones pancreatic polypeptide, insulin, glucagon, and somatostatin.

### Pancreatic Juice

The pancreas produces over a liter of pancreatic juice each day. Unlike bile, it is clear and composed mostly of water along with some salts, sodium bicarbonate, and several digestive enzymes. Sodium bicarbonate is responsible for the slight alkalinity of pancreatic juice (pH 7.1 to 8.2), which serves to buffer the acidic gastric juice in chyme, inactivate pepsin from the stomach, and create an optimal environment for the activity of pH-sensitive digestive enzymes in the small intestine. Pancreatic enzymes are active in the digestion of sugars, proteins, and fats.

The pancreas produces protein-digesting enzymes in their inactive forms. These enzymes are activated in the duodenum. If produced in an active form, they would digest the pancreas (which is exactly what occurs in the disease, pancreatitis). The intestinal brush border enzyme **enteropeptidase** stimulates the activation of trypsin from trypsinogen of the pancreas, which in turn changes the pancreatic enzymes procarboxypeptidase and chymotrypsinogen into their active forms, carboxypeptidase and chymotrypsin.

The enzymes that digest starch (amylase), fat (lipase), and nucleic acids (nuclease) are secreted in their active forms, since they do not attack the pancreas as do the protein-digesting enzymes.

## Pancreatic Secretion

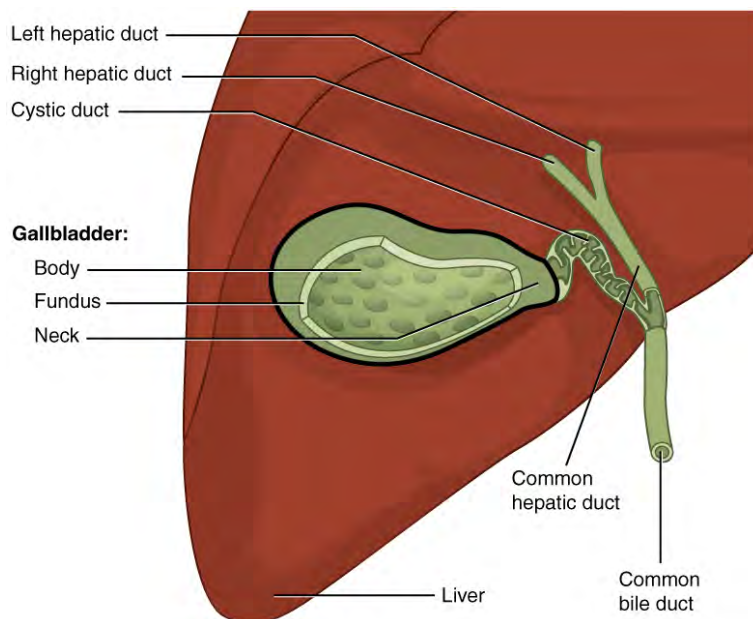
Regulation of pancreatic secretion is the job of hormones and the parasympathetic nervous system. The entry of acidic chyme into the duodenum stimulates the release of secretin, which in turn causes the duct cells to release bicarbonate-rich pancreatic juice. The presence of proteins and fats in the duodenum stimulates the secretion of CCK, which then stimulates the acini to secrete enzyme-rich pancreatic juice and enhances the activity of secretin. Parasympathetic regulation occurs mainly during the cephalic and gastric phases of gastric secretion, when vagal stimulation prompts the secretion of pancreatic juice.

Usually, the pancreas secretes just enough bicarbonate to counterbalance the amount of HCl produced in the stomach. Hydrogen ions enter the blood when bicarbonate is secreted by the pancreas. Thus, the acidic blood draining from the pancreas neutralizes the alkaline blood draining from the stomach, maintaining the pH of the venous blood that flows to the liver.

## The Gallbladder

The **gallbladder** is 8–10 cm (~3–4 in) long and is nestled in a shallow area on the posterior aspect of the right lobe of the liver. This muscular sac stores, concentrates, and, when stimulated, propels the bile into the duodenum via the common bile duct. It is divided into three regions. The fundus is the widest portion and tapers medially into the body, which in turn narrows to become the neck. The neck angles slightly superiorly as it approaches the hepatic duct. The cystic duct is 1–2 cm (less than 1 in) long and turns inferiorly as it bridges the neck and hepatic duct.

The simple columnar epithelium of the gallbladder mucosa is organized in rugae, similar to those of the stomach. There is no submucosa in the gallbladder wall. The wall's middle, muscular coat is made of smooth muscle fibers. When these fibers contract, the gallbladder's contents are ejected through the **cystic duct** and into the bile duct (**Figure 23.27**). Visceral peritoneum reflected from the liver capsule holds the gallbladder against the liver and forms the outer coat of the gallbladder. The gallbladder's mucosa absorbs water and ions from bile, concentrating it by up to 10-fold.



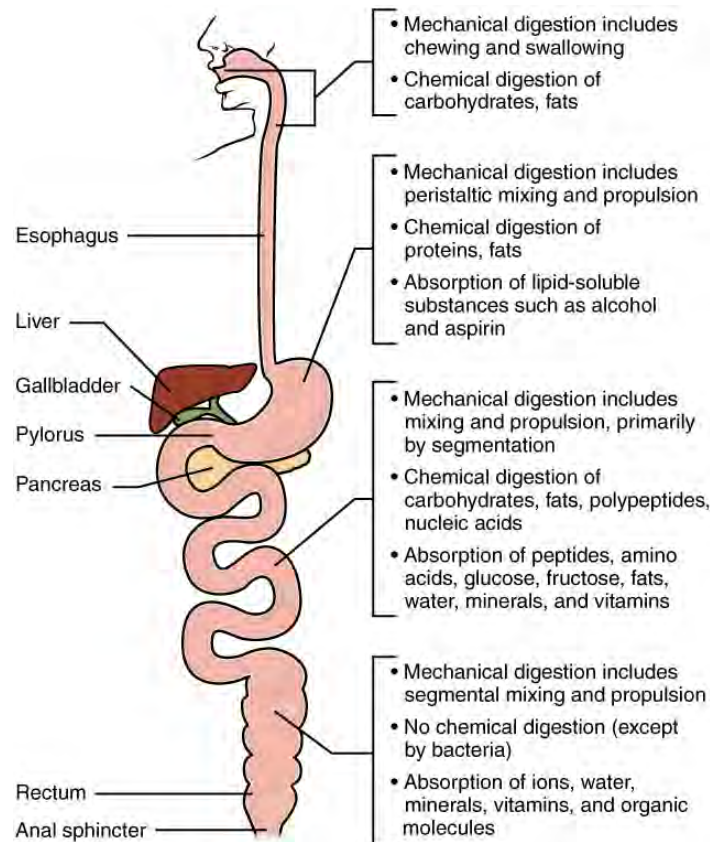
**Figure 23.27 Gallbladder** The gallbladder stores and concentrates bile, and releases it into the two-way cystic duct when it is needed by the small intestine.

## 23.7 | Chemical Digestion and Absorption: A Closer Look

By the end of this section, you will be able to:

- Identify the locations and primary secretions involved in the chemical digestion of carbohydrates, proteins, lipids, and nucleic acids
- Compare and contrast absorption of the hydrophilic and hydrophobic nutrients

As you have learned, the process of mechanical digestion is relatively simple. It involves the physical breakdown of food but does not alter its chemical makeup. Chemical digestion, on the other hand, is a complex process that reduces food into its chemical building blocks, which are then absorbed to nourish the cells of the body (**Figure 23.28**). In this section, you will look more closely at the processes of chemical digestion and absorption.



**Figure 23.28 Digestion and Absorption** Digestion begins in the mouth and continues as food travels through the small intestine. Most absorption occurs in the small intestine.

### Chemical Digestion

Large food molecules (for example, proteins, lipids, nucleic acids, and starches) must be broken down into subunits that are small enough to be absorbed by the lining of the alimentary canal. This is accomplished by enzymes through hydrolysis. The many enzymes involved in chemical digestion are summarized in **Table 23.8**.

## The Digestive Enzymes

Enzyme Category	Enzyme Name	Source	Substrate	Product
Salivary Enzymes	Lingual lipase	Lingual glands	Triglycerides	Free fatty acids, and mono- and diglycerides
Salivary Enzymes	Salivary amylase	Salivary glands	Polysaccharides	Disaccharides and trisaccharides
Gastric enzymes	Gastric lipase	Chief cells	Triglycerides	Fatty acids and monoacylglycerides
Gastric enzymes	Pepsin*	Chief cells	Proteins	Peptides
Brush border enzymes	$\alpha$ -Dextrinase	Small intestine	$\alpha$ -Dextrins	Glucose
Brush border enzymes	Enteropeptidase	Small intestine	Trypsinogen	Trypsin
Brush border enzymes	Lactase	Small intestine	Lactose	Glucose and galactose
Brush border enzymes	Maltase	Small intestine	Maltose	Glucose
Brush border enzymes	Nucleosidases and phosphatases	Small intestine	Nucleotides	Phosphates, nitrogenous bases, and pentoses
Brush border enzymes	Peptidases	Small intestine	Aminopeptidase: amino acids at the amino end of peptides Dipeptidase: dipeptides	Aminopeptidase: amino acids and peptides Dipeptidase: amino acids
Brush border enzymes	Sucrase	Small intestine	Sucrose	Glucose and fructose
Pancreatic enzymes	Carboxypeptidase*	Pancreatic acinar cells	Amino acids at the carboxyl end of peptides	Amino acids and peptides
Pancreatic enzymes	Chymotrypsin*	Pancreatic acinar cells	Proteins	Peptides
Pancreatic enzymes	Elastase*	Pancreatic acinar cells	Proteins	Peptides
Pancreatic enzymes	Nucleases	Pancreatic acinar cells	Ribonuclease: ribonucleic acids Deoxyribonuclease: deoxyribonucleic acids	Nucleotides
Pancreatic enzymes	Pancreatic amylase	Pancreatic acinar cells	Polysaccharides (starches)	$\alpha$ -Dextrins, disaccharides (maltose), trisaccharides (maltotriose)
Pancreatic enzymes	Pancreatic lipase	Pancreatic acinar cells	Triglycerides that have been emulsified by bile salts	Fatty acids and monoacylglycerides
Pancreatic enzymes	Trypsin*	Pancreatic acinar cells	Proteins	Peptides

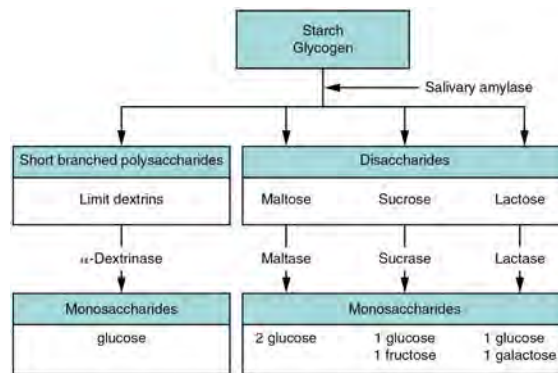
**Table 23.8** \*These enzymes have been activated by other substances.

## Carbohydrate Digestion

The average American diet is about 50 percent carbohydrates, which may be classified according to the number of monomers they contain of simple sugars (monosaccharides and disaccharides) and/or complex sugars (polysaccharides). Glucose, galactose, and fructose are the three monosaccharides that are commonly consumed and are readily absorbed. Your digestive system is also able to break down the disaccharide sucrose (regular table sugar: glucose + fructose), lactose (milk sugar: glucose + galactose), and maltose (grain sugar: glucose + glucose), and the polysaccharides glycogen and starch (chains of monosaccharides). Your bodies do not produce enzymes that can break down most fibrous polysaccharides, such as cellulose. While indigestible polysaccharides do not provide any nutritional value, they do provide dietary fiber, which helps propel food through the alimentary canal.

The chemical digestion of starches begins in the mouth and has been reviewed above.

In the small intestine, **pancreatic amylase** does the ‘heavy lifting’ for starch and carbohydrate digestion (**Figure 23.29**). After amylases break down starch into smaller fragments, the brush border enzyme  **$\alpha$ -dextrinase** starts working on  **$\alpha$ -dextrin**, breaking off one glucose unit at a time. Three brush border enzymes hydrolyze sucrose, lactose, and maltose into monosaccharides. **Sucrase** splits sucrose into one molecule of fructose and one molecule of glucose; **maltase** breaks down maltose and maltotriose into two and three glucose molecules, respectively; and **lactase** breaks down lactose into one molecule of glucose and one molecule of galactose. Insufficient lactase can lead to lactose intolerance.

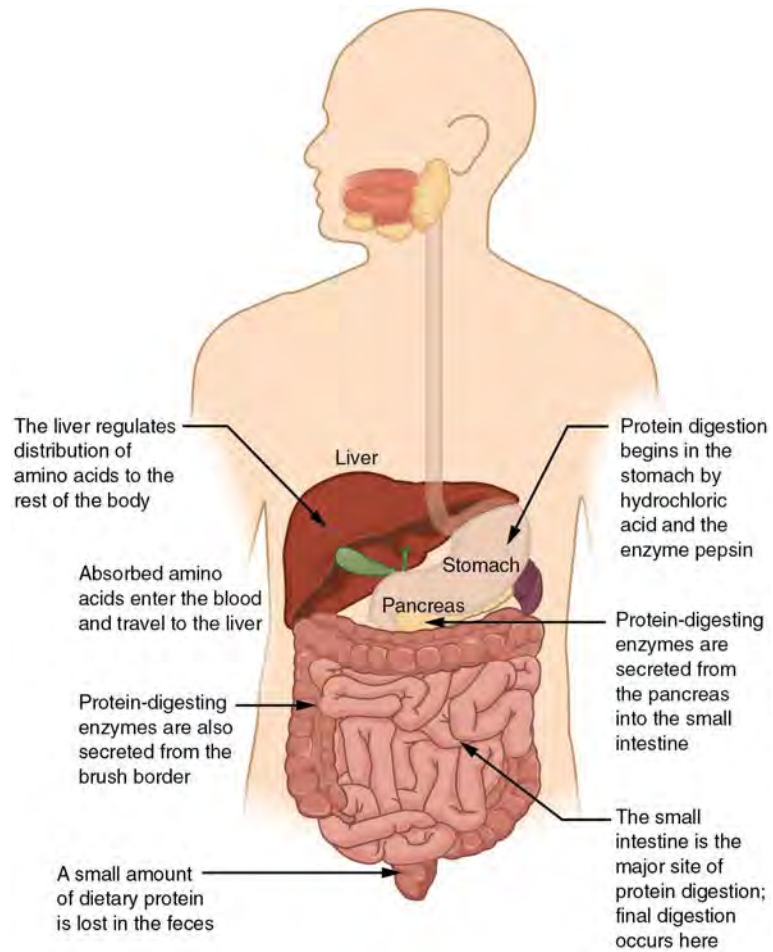


**Figure 23.29 Carbohydrate Digestion Flow Chart** Carbohydrates are broken down into their monomers in a series of steps.

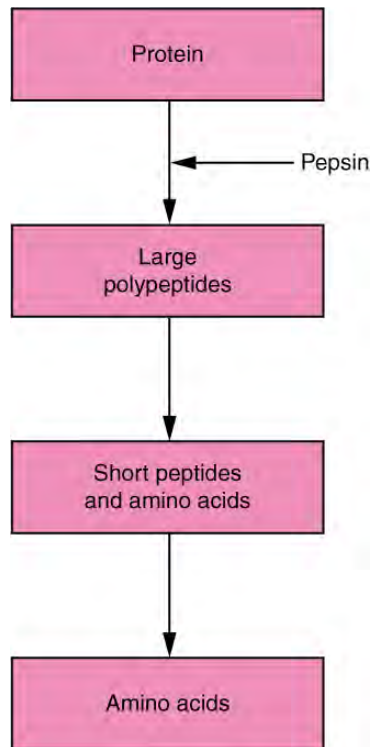
## Protein Digestion

Proteins are polymers composed of amino acids linked by peptide bonds to form long chains. Digestion reduces them to their constituent amino acids. You usually consume about 15 to 20 percent of your total calorie intake as protein.

The digestion of protein starts in the stomach, where HCl and pepsin break proteins into smaller polypeptides, which then travel to the small intestine (**Figure 23.30**). Chemical digestion in the small intestine is continued by pancreatic enzymes, including chymotrypsin and trypsin, each of which act on specific bonds in amino acid sequences. At the same time, the cells of the brush border secrete enzymes such as **aminopeptidase** and **dipeptidase**, which further break down peptide chains. This results in molecules small enough to enter the bloodstream (**Figure 23.31**).



**Figure 23.30 Digestion of Protein** The digestion of protein begins in the stomach and is completed in the small intestine.



**Figure 23.31 Digestion of Protein Flow Chart** Proteins are successively broken down into their amino acid components.

### Lipid Digestion

A healthy diet limits lipid intake to 35 percent of total calorie intake. The most common dietary lipids are triglycerides, which are made up of a glycerol molecule bound to three fatty acid chains. Small amounts of dietary cholesterol and phospholipids are also consumed.

The three lipases responsible for lipid digestion are lingual lipase, gastric lipase, and **pancreatic lipase**. However, because the pancreas is the only consequential source of lipase, virtually all lipid digestion occurs in the small intestine. Pancreatic lipase breaks down each triglyceride into two free fatty acids and a monoglyceride. The fatty acids include both short-chain (less than 10 to 12 carbons) and long-chain fatty acids.

### Nucleic Acid Digestion

The nucleic acids DNA and RNA are found in most of the foods you eat. Two types of **pancreatic nuclease** are responsible for their digestion: **deoxyribonuclease**, which digests DNA, and **ribonuclease**, which digests RNA. The nucleotides produced by this digestion are further broken down by two intestinal brush border enzymes ( **nucleosidase** and **phosphatase**) into pentoses, phosphates, and nitrogenous bases, which can be absorbed through the alimentary canal wall. The large food molecules that must be broken down into subunits are summarized **Table 23.9**

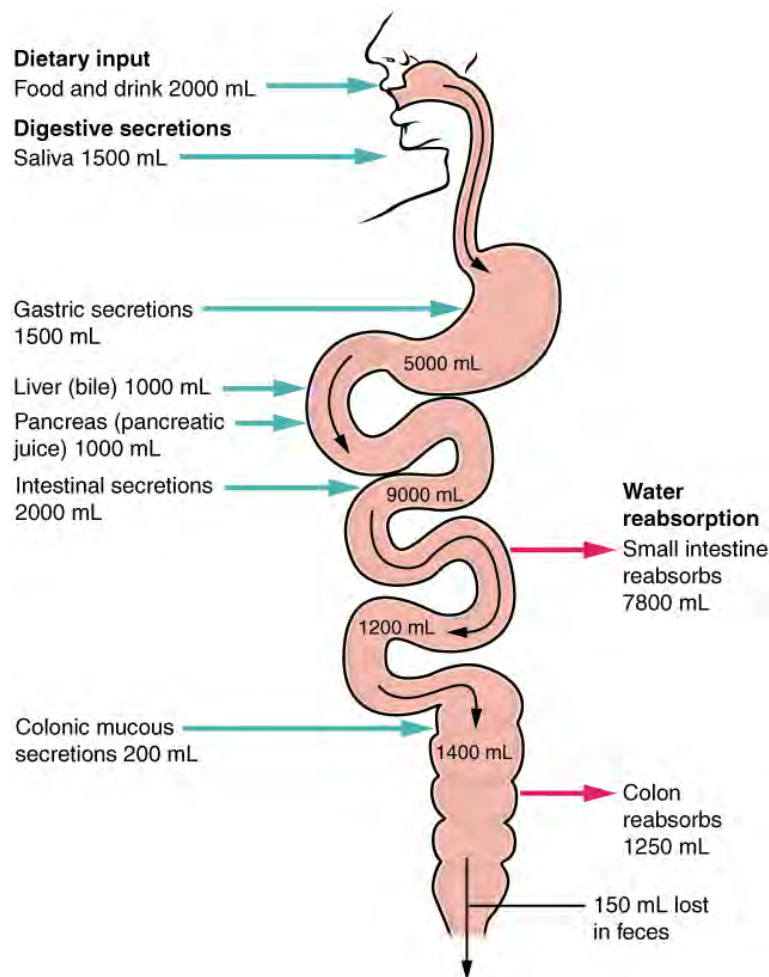
### Absorbable Food Substances

Source	Substance
Carbohydrates	Monosaccharides: glucose, galactose, and fructose
Proteins	Single amino acids, dipeptides, and tripeptides
Triglycerides	Monoacylglycerides, glycerol, and free fatty acids
Nucleic acids	Pentose sugars, phosphates, and nitrogenous bases

**Table 23.9**

## Absorption

The mechanical and digestive processes have one goal: to convert food into molecules small enough to be absorbed by the epithelial cells of the intestinal villi. The absorptive capacity of the alimentary canal is almost endless. Each day, the alimentary canal processes up to 10 liters of food, liquids, and GI secretions, yet less than one liter enters the large intestine. Almost all ingested food, 80 percent of electrolytes, and 90 percent of water are absorbed in the small intestine. Although the entire small intestine is involved in the absorption of water and lipids, most absorption of carbohydrates and proteins occurs in the jejunum. Notably, bile salts and vitamin B<sub>12</sub> are absorbed in the terminal ileum. By the time chyme passes from the ileum into the large intestine, it is essentially indigestible food residue (mainly plant fibers like cellulose), some water, and millions of bacteria (**Figure 23.32**).



**Figure 23.32 Digestive Secretions and Absorption of Water** Absorption is a complex process, in which nutrients from digested food are harvested.

Absorption can occur through five mechanisms: (1) active transport, (2) passive diffusion, (3) facilitated diffusion, (4) co-transport (or secondary active transport), and (5) endocytosis. As you will recall from Chapter 3, active transport refers to the movement of a substance across a cell membrane going from an area of lower concentration to an area of higher concentration (up the concentration gradient). In this type of transport, proteins within the cell membrane act as “pumps,” using cellular energy (ATP) to move the substance. Passive diffusion refers to the movement of substances from an area of higher concentration to an area of lower concentration, while facilitated diffusion refers to the movement of substances from an area of higher to an area of lower concentration using a carrier protein in the cell membrane. Co-transport uses the movement of one molecule through the membrane from higher to lower concentration to power the movement of another from lower to higher. Finally, endocytosis is a transportation process in which the cell membrane engulfs material. It requires energy, generally in the form of ATP.

Because the cell’s plasma membrane is made up of hydrophobic phospholipids, water-soluble nutrients must use transport

molecules embedded in the membrane to enter cells. Moreover, substances cannot pass between the epithelial cells of the intestinal mucosa because these cells are bound together by tight junctions. Thus, substances can only enter blood capillaries by passing through the apical surfaces of epithelial cells and into the interstitial fluid. Water-soluble nutrients enter the capillary blood in the villi and travel to the liver via the hepatic portal vein.

In contrast to the water-soluble nutrients, lipid-soluble nutrients can diffuse through the plasma membrane. Once inside the cell, they are packaged for transport via the base of the cell and then enter the lacteals of the villi to be transported by lymphatic vessels to the systemic circulation via the thoracic duct. The absorption of most nutrients through the mucosa of the intestinal villi requires active transport fueled by ATP. The routes of absorption for each food category are summarized in **Table 23.10**.

### Absorption in the Alimentary Canal

Food	Breakdown products	Absorption mechanism	Entry to bloodstream	Destination
Carbohydrates	Glucose	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein
Carbohydrates	Galactose	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein
Carbohydrates	Fructose	Facilitated diffusion	Capillary blood in villi	Liver via hepatic portal vein
Protein	Amino acids	Co-transport with sodium ions	Capillary blood in villi	Liver via hepatic portal vein
Lipids	Long-chain fatty acids	Diffusion into intestinal cells, where they are combined with proteins to create chylomicrons	Lacteals of villi	Systemic circulation via lymph entering thoracic duct
Lipids	Monoacylglycerides	Diffusion into intestinal cells, where they are combined with proteins to create chylomicrons	Lacteals of villi	Systemic circulation via lymph entering thoracic duct
Lipids	Short-chain fatty acids	Simple diffusion	Capillary blood in villi	Liver via hepatic portal vein
Lipids	Glycerol	Simple diffusion	Capillary blood in villi	Liver via hepatic portal vein
Nucleic Acids	Nucleic acid digestion products	Active transport via membrane carriers	Capillary blood in villi	Liver via hepatic portal vein

**Table 23.10**

#### Carbohydrate Absorption

All carbohydrates are absorbed in the form of monosaccharides. The small intestine is highly efficient at this, absorbing monosaccharides at an estimated rate of 120 grams per hour. All normally digested dietary carbohydrates are absorbed; indigestible fibers are eliminated in the feces. The monosaccharides glucose and galactose are transported into the epithelial cells by common protein carriers via secondary active transport (that is, co-transport with sodium ions). The monosaccharides leave these cells via facilitated diffusion and enter the capillaries through intercellular clefts. The monosaccharide fructose (which is in fruit) is absorbed and transported by facilitated diffusion alone. The monosaccharides combine with the transport proteins immediately after the disaccharides are broken down.

#### Protein Absorption

Active transport mechanisms, primarily in the duodenum and jejunum, absorb most proteins as their breakdown products, amino acids. Almost all (95 to 98 percent) protein is digested and absorbed in the small intestine. The type of carrier that transports an amino acid varies. Most carriers are linked to the active transport of sodium. Short chains of two amino

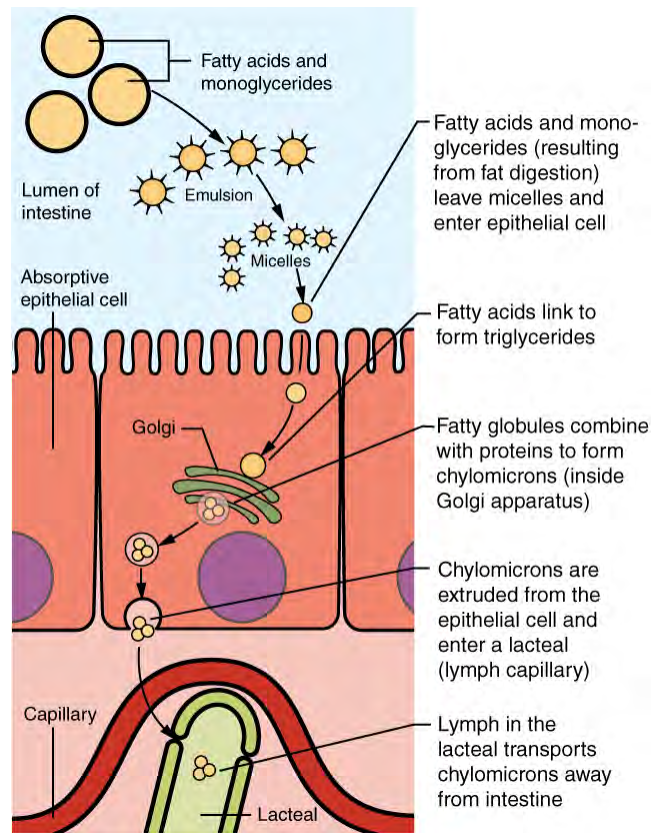
acids (dipeptides) or three amino acids (tripeptides) are also transported actively. However, after they enter the absorptive epithelial cells, they are broken down into their amino acids before leaving the cell and entering the capillary blood via diffusion.

### Lipid Absorption

About 95 percent of lipids are absorbed in the small intestine. Bile salts not only speed up lipid digestion, they are also essential to the absorption of the end products of lipid digestion. Short-chain fatty acids are relatively water soluble and can enter the absorptive cells (enterocytes) directly. The small size of short-chain fatty acids enables them to be absorbed by enterocytes via simple diffusion, and then take the same path as monosaccharides and amino acids into the blood capillary of a villus.

The large and hydrophobic long-chain fatty acids and monoacylglycerides are not so easily suspended in the watery intestinal chyme. However, bile salts and lecithin resolve this issue by enclosing them in a **micelle**, which is a tiny sphere with polar (hydrophilic) ends facing the watery environment and hydrophobic tails turned to the interior, creating a receptive environment for the long-chain fatty acids. The core also includes cholesterol and fat-soluble vitamins. Without micelles, lipids would sit on the surface of chyme and never come in contact with the absorptive surfaces of the epithelial cells. Micelles can easily squeeze between microvilli and get very near the luminal cell surface. At this point, lipid substances exit the micelle and are absorbed via simple diffusion.

The free fatty acids and monoacylglycerides that enter the epithelial cells are reincorporated into triglycerides. The triglycerides are mixed with phospholipids and cholesterol, and surrounded with a protein coat. This new complex, called a **chylomicron**, is a water-soluble lipoprotein. After being processed by the Golgi apparatus, chylomicrons are released from the cell (**Figure 23.33**). Too big to pass through the basement membranes of blood capillaries, chylomicrons instead enter the large pores of lacteals. The lacteals come together to form the lymphatic vessels. The chylomicrons are transported in the lymphatic vessels and empty through the thoracic duct into the subclavian vein of the circulatory system. Once in the bloodstream, the enzyme **lipoprotein lipase** breaks down the triglycerides of the chylomicrons into free fatty acids and glycerol. These breakdown products then pass through capillary walls to be used for energy by cells or stored in adipose tissue as fat. Liver cells combine the remaining chylomicron remnants with proteins, forming lipoproteins that transport cholesterol in the blood.



**Figure 23.33 Lipid Absorption** Unlike amino acids and simple sugars, lipids are transformed as they are absorbed through epithelial cells.

### Nucleic Acid Absorption

The products of nucleic acid digestion—pentose sugars, nitrogenous bases, and phosphate ions—are transported by carriers across the villus epithelium via active transport. These products then enter the bloodstream.

### Mineral Absorption

The electrolytes absorbed by the small intestine are from both GI secretions and ingested foods. Since electrolytes dissociate into ions in water, most are absorbed via active transport throughout the entire small intestine. During absorption, co-transport mechanisms result in the accumulation of sodium ions inside the cells, whereas anti-transport mechanisms reduce the potassium ion concentration inside the cells. To restore the sodium-potassium gradient across the cell membrane, a sodium-potassium pump requiring ATP pumps sodium out and potassium in.

In general, all minerals that enter the intestine are absorbed, whether you need them or not. Iron and calcium are exceptions; they are absorbed in the duodenum in amounts that meet the body's current requirements, as follows:

**Iron**—The ionic iron needed for the production of hemoglobin is absorbed into mucosal cells via active transport. Once inside mucosal cells, ionic iron binds to the protein ferritin, creating iron-ferritin complexes that store iron until needed. When the body has enough iron, most of the stored iron is lost when worn-out epithelial cells slough off. When the body needs iron because, for example, it is lost during acute or chronic bleeding, there is increased uptake of iron from the intestine and accelerated release of iron into the bloodstream. Since women experience significant iron loss during menstruation, they have around four times as many iron transport proteins in their intestinal epithelial cells as do men.

**Calcium**—Blood levels of ionic calcium determine the absorption of dietary calcium. When blood levels of ionic calcium drop, parathyroid hormone (PTH) secreted by the parathyroid glands stimulates the release of calcium ions from bone matrices and increases the reabsorption of calcium by the kidneys. PTH also upregulates the activation of vitamin D in the kidney, which then facilitates intestinal calcium ion absorption.

### Vitamin Absorption

The small intestine absorbs the vitamins that occur naturally in food and supplements. Fat-soluble vitamins (A, D, E, and K)

are absorbed along with dietary lipids in micelles via simple diffusion. This is why you are advised to eat some fatty foods when you take fat-soluble vitamin supplements. Most water-soluble vitamins (including most B vitamins and vitamin C) also are absorbed by simple diffusion. An exception is vitamin B<sub>12</sub>, which is a very large molecule. Intrinsic factor secreted in the stomach binds to vitamin B<sub>12</sub>, preventing its digestion and creating a complex that binds to mucosal receptors in the terminal ileum, where it is taken up by endocytosis.

### Water Absorption

Each day, about nine liters of fluid enter the small intestine. About 2.3 liters are ingested in foods and beverages, and the rest is from GI secretions. About 90 percent of this water is absorbed in the small intestine. Water absorption is driven by the concentration gradient of the water: The concentration of water is higher in chyme than it is in epithelial cells. Thus, water moves down its concentration gradient from the chyme into cells. As noted earlier, much of the remaining water is then absorbed in the colon.

## KEY TERMS

**absorption** passage of digested products from the intestinal lumen through mucosal cells and into the bloodstream or lacteals

**accessory digestive organ** includes teeth, tongue, salivary glands, gallbladder, liver, and pancreas

**accessory duct** (also, duct of Santorini) duct that runs from the pancreas into the duodenum

**acinus** cluster of glandular epithelial cells in the pancreas that secretes pancreatic juice in the pancreas

**alimentary canal** continuous muscular digestive tube that extends from the mouth to the anus

**aminopeptidase** brush border enzyme that acts on proteins

**anal canal** final segment of the large intestine

**anal column** long fold of mucosa in the anal canal

**anal sinus** recess between anal columns

**appendix** (vermiform appendix) coiled tube attached to the cecum

**ascending colon** first region of the colon

**bacterial flora** bacteria in the large intestine

**bile** alkaline solution produced by the liver and important for the emulsification of lipids

**bile canaliculus** small duct between hepatocytes that collects bile

**bilirubin** main bile pigment, which is responsible for the brown color of feces

**body** mid-portion of the stomach

**bolus** mass of chewed food

**brush border** fuzzy appearance of the small intestinal mucosa created by microvilli

**cardia** (also, cardiac region) part of the stomach surrounding the cardiac orifice (esophageal hiatus)

**cecum** pouch forming the beginning of the large intestine

**cementum** bone-like tissue covering the root of a tooth

**central vein** vein that receives blood from hepatic sinusoids

**cephalic phase** (also, reflex phase) initial phase of gastric secretion that occurs before food enters the stomach

**chemical digestion** enzymatic breakdown of food

**chief cell** gastric gland cell that secretes pepsinogen

**chylomicron** large lipid-transport compound made up of triglycerides, phospholipids, cholesterol, and proteins

**chyme** soupy liquid created when food is mixed with digestive juices

**circular fold** (also, plica circulares) deep fold in the mucosa and submucosa of the small intestine

**colon** part of the large intestine between the cecum and the rectum

**common bile duct** structure formed by the union of the common hepatic duct and the gallbladder's cystic duct

**common hepatic duct** duct formed by the merger of the two hepatic ducts

**crown** portion of tooth visible superior to the gum line

**cuspid** (also, canine) pointed tooth used for tearing and shredding food

**cystic duct** duct through which bile drains and enters the gallbladder

**deciduous tooth** one of 20 “baby teeth”

**defecation** elimination of undigested substances from the body in the form of feces

**deglutition** three-stage process of swallowing

**dens** tooth

**dentin** bone-like tissue immediately deep to the enamel of the crown or cementum of the root of a tooth

**dentition** set of teeth

**deoxyribonuclease** pancreatic enzyme that digests DNA

**descending colon** part of the colon between the transverse colon and the sigmoid colon

**dipeptidase** brush border enzyme that acts on dipeptides

**duodenal gland** (also, Brunner’s gland) mucous-secreting gland in the duodenal submucosa

**duodenum** first part of the small intestine, which starts at the pyloric sphincter and ends at the jejunum

**enamel** covering of the dentin of the crown of a tooth

**enteroendocrine cell** gastric gland cell that releases hormones

**enterohepatic circulation** recycling mechanism that conserves bile salts

**enteropeptidase** intestinal brush-border enzyme that activates trypsinogen to trypsin

**epiploic appendage** small sac of fat-filled visceral peritoneum attached to teniae coli

**esophagus** muscular tube that runs from the pharynx to the stomach

**external anal sphincter** voluntary skeletal muscle sphincter in the anal canal

**fauces** opening between the oral cavity and the oropharynx

**feces** semisolid waste product of digestion

**flatus** gas in the intestine

**fundus** dome-shaped region of the stomach above and to the left of the cardia

**G cell** gastrin-secreting enteroendocrine cell

**gallbladder** accessory digestive organ that stores and concentrates bile

**gastric emptying** process by which mixing waves gradually cause the release of chyme into the duodenum

**gastric gland** gland in the stomach mucosal epithelium that produces gastric juice

**gastric phase** phase of gastric secretion that begins when food enters the stomach

**gastric pit** narrow channel formed by the epithelial lining of the stomach mucosa

**gastrin** peptide hormone that stimulates secretion of hydrochloric acid and gut motility

- gastrocolic reflex** propulsive movement in the colon activated by the presence of food in the stomach
- gastroileal reflex** long reflex that increases the strength of segmentation in the ileum
- gingiva** gum
- haustral contraction** slow segmentation in the large intestine
- haustrum** small pouch in the colon created by tonic contractions of teniae coli
- hepatic artery** artery that supplies oxygenated blood to the liver
- hepatic lobule** hexagonal-shaped structure composed of hepatocytes that radiate outward from a central vein
- hepatic portal vein** vein that supplies deoxygenated nutrient-rich blood to the liver
- hepatic sinusoid** blood capillaries between rows of hepatocytes that receive blood from the hepatic portal vein and the branches of the hepatic artery
- hepatic vein** vein that drains into the inferior vena cava
- hepatocytes** major functional cells of the liver
- hepatopancreatic ampulla** (also, ampulla of Vater) bulb-like point in the wall of the duodenum where the bile duct and main pancreatic duct unite
- hepatopancreatic sphincter** (also, sphincter of Oddi) sphincter regulating the flow of bile and pancreatic juice into the duodenum
- hydrochloric acid (HCl)** digestive acid secreted by parietal cells in the stomach
- ileocecal sphincter** sphincter located where the small intestine joins with the large intestine
- ileum** end of the small intestine between the jejunum and the large intestine
- incisor** midline, chisel-shaped tooth used for cutting into food
- ingestion** taking food into the GI tract through the mouth
- internal anal sphincter** involuntary smooth muscle sphincter in the anal canal
- intestinal gland** (also, crypt of Lieberkühn) gland in the small intestinal mucosa that secretes intestinal juice
- intestinal juice** mixture of water and mucus that helps absorb nutrients from chyme
- intestinal phase** phase of gastric secretion that begins when chyme enters the intestine
- intrinsic factor** glycoprotein required for vitamin B<sub>12</sub> absorption in the small intestine
- jejunum** middle part of the small intestine between the duodenum and the ileum
- labial frenulum** midline mucous membrane fold that attaches the inner surface of the lips to the gums
- labium** lip
- lactase** brush border enzyme that breaks down lactose into glucose and galactose
- lacteal** lymphatic capillary in the villi
- large intestine** terminal portion of the alimentary canal
- laryngopharynx** part of the pharynx that functions in respiration and digestion
- left colic flexure** (also, splenic flexure) point where the transverse colon curves below the inferior end of the spleen

- lingual frenulum** mucous membrane fold that attaches the bottom of the tongue to the floor of the mouth
- lingual lipase** digestive enzyme from glands in the tongue that acts on triglycerides
- lipoprotein lipase** enzyme that breaks down triglycerides in chylomicrons into fatty acids and monoglycerides
- liver** largest gland in the body whose main digestive function is the production of bile
- lower esophageal sphincter** smooth muscle sphincter that regulates food movement from the esophagus to the stomach
- main pancreatic duct** (also, duct of Wirsung) duct through which pancreatic juice drains from the pancreas
- major duodenal papilla** point at which the hepatopancreatic ampulla opens into the duodenum
- maltase** brush border enzyme that breaks down maltose and maltotriose into two and three molecules of glucose, respectively
- mass movement** long, slow, peristaltic wave in the large intestine
- mastication** chewing
- mechanical digestion** chewing, mixing, and segmentation that prepares food for chemical digestion
- mesoappendix** mesentery of the appendix
- micelle** tiny lipid-transport compound composed of bile salts and phospholipids with a fatty acid and monoacylglyceride core
- microvillus** small projection of the plasma membrane of the absorptive cells of the small intestinal mucosa
- migrating motility complex** form of peristalsis in the small intestine
- mixing wave** unique type of peristalsis that occurs in the stomach
- molar** tooth used for crushing and grinding food
- motilin** hormone that initiates migrating motility complexes
- motility** movement of food through the GI tract
- mucosa** innermost lining of the alimentary canal
- mucosal barrier** protective barrier that prevents gastric juice from destroying the stomach itself
- mucous neck cell** gastric gland cell that secretes a uniquely acidic mucus
- muscularis** muscle (skeletal or smooth) layer of the alimentary canal wall
- myenteric plexus** (plexus of Auerbach) major nerve supply to alimentary canal wall; controls motility
- nucleosidase** brush border enzyme that digests nucleotides
- oral cavity** (also, buccal cavity) mouth
- oral vestibule** part of the mouth bounded externally by the cheeks and lips, and internally by the gums and teeth
- oropharynx** part of the pharynx continuous with the oral cavity that functions in respiration and digestion
- palatoglossal arch** muscular fold that extends from the lateral side of the soft palate to the base of the tongue
- palatopharyngeal arch** muscular fold that extends from the lateral side of the soft palate to the side of the pharynx
- pancreas** accessory digestive organ that secretes pancreatic juice

- pancreatic amylase** enzyme secreted by the pancreas that completes the chemical digestion of carbohydrates in the small intestine
- pancreatic juice** secretion of the pancreas containing digestive enzymes and bicarbonate
- pancreatic lipase** enzyme secreted by the pancreas that participates in lipid digestion
- pancreatic nuclease** enzyme secreted by the pancreas that participates in nucleic acid digestion
- parietal cell** gastric gland cell that secretes hydrochloric acid and intrinsic factor
- parotid gland** one of a pair of major salivary glands located inferior and anterior to the ears
- pectinate line** horizontal line that runs like a ring, perpendicular to the inferior margins of the anal sinuses
- pepsinogen** inactive form of pepsin
- peristalsis** muscular contractions and relaxations that propel food through the GI tract
- permanent tooth** one of 32 adult teeth
- pharynx** throat
- phosphatase** brush border enzyme that digests nucleotides
- porta hepatis** “gateway to the liver” where the hepatic artery and hepatic portal vein enter the liver
- portal triad** bile duct, hepatic artery branch, and hepatic portal vein branch
- premolar** (also, bicuspid) transitional tooth used for mastication, crushing, and grinding food
- propulsion** voluntary process of swallowing and the involuntary process of peristalsis that moves food through the digestive tract
- pulp cavity** deepest portion of a tooth, containing nerve endings and blood vessels
- pyloric antrum** wider, more superior part of the pylorus
- pyloric canal** narrow, more inferior part of the pylorus
- pyloric sphincter** sphincter that controls stomach emptying
- pylorus** lower, funnel-shaped part of the stomach that is continuous with the duodenum
- rectal valve** one of three transverse folds in the rectum where feces is separated from flatus
- rectum** part of the large intestine between the sigmoid colon and anal canal
- reticuloendothelial cell** (also, Kupffer cell) phagocyte in hepatic sinusoids that filters out material from venous blood from the alimentary canal
- retroperitoneal** located posterior to the peritoneum
- ribonuclease** pancreatic enzyme that digests RNA
- right colic flexure** (also, hepatic flexure) point, at the inferior surface of the liver, where the ascending colon turns abruptly to the left
- root** portion of a tooth embedded in the alveolar processes beneath the gum line
- ruqa** fold of alimentary canal mucosa and submucosa in the empty stomach and other organs
- saccharolytic fermentation** anaerobic decomposition of carbohydrates

- saliva** aqueous solution of proteins and ions secreted into the mouth by the salivary glands
- salivary amylase** digestive enzyme in saliva that acts on starch
- salivary gland** an exocrine gland that secretes a digestive fluid called saliva
- salivation** secretion of saliva
- segmentation** alternating contractions and relaxations of non-adjacent segments of the intestine that move food forward and backward, breaking it apart and mixing it with digestive juices
- serosa** outermost layer of the alimentary canal wall present in regions within the abdominal cavity
- sigmoid colon** end portion of the colon, which terminates at the rectum
- small intestine** section of the alimentary canal where most digestion and absorption occurs
- soft palate** posterior region of the bottom portion of the nasal cavity that consists of skeletal muscle
- stomach** alimentary canal organ that contributes to chemical and mechanical digestion of food from the esophagus before releasing it, as chyme, to the small intestine
- sublingual gland** one of a pair of major salivary glands located beneath the tongue
- submandibular gland** one of a pair of major salivary glands located in the floor of the mouth
- submucosa** layer of dense connective tissue in the alimentary canal wall that binds the overlying mucosa to the underlying muscularis
- submucosal plexus** (plexus of Meissner) nerve supply that regulates activity of glands and smooth muscle
- sucrase** brush border enzyme that breaks down sucrose into glucose and fructose
- tenia coli** one of three smooth muscle bands that make up the longitudinal muscle layer of the muscularis in all of the large intestine except the terminal end
- tongue** accessory digestive organ of the mouth, the bulk of which is composed of skeletal muscle
- transverse colon** part of the colon between the ascending colon and the descending colon
- upper esophageal sphincter** skeletal muscle sphincter that regulates food movement from the pharynx to the esophagus
- Valsalva's maneuver** voluntary contraction of the diaphragm and abdominal wall muscles and closing of the glottis, which increases intra-abdominal pressure and facilitates defecation
- villus** projection of the mucosa of the small intestine
- voluntary phase** initial phase of deglutition, in which the bolus moves from the mouth to the oropharynx
- $\alpha$ -dextrin** breakdown product of starch
- $\alpha$ -dextrinase** brush border enzyme that acts on  $\alpha$ -dextrins

## CHAPTER REVIEW

### 23.1 Overview of the Digestive System

The digestive system includes the organs of the alimentary canal and accessory structures. The alimentary canal forms a continuous tube that is open to the outside environment at both ends. The organs of the alimentary canal are the mouth, pharynx, esophagus, stomach, small intestine, and large intestine. The accessory digestive structures include the teeth, tongue, salivary glands, liver, pancreas, and gallbladder. The wall of the alimentary canal is composed of four basic tissue layers: mucosa, submucosa, muscularis, and serosa. The enteric nervous system provides intrinsic innervation, and the

autonomic nervous system provides extrinsic innervation.

## 23.2 Digestive System Processes and Regulation

The digestive system ingests and digests food, absorbs released nutrients, and excretes food components that are indigestible. The six activities involved in this process are ingestion, motility, mechanical digestion, chemical digestion, absorption, and defecation. These processes are regulated by neural and hormonal mechanisms.

## 23.3 The Mouth, Pharynx, and Esophagus

In the mouth, the tongue and the teeth begin mechanical digestion, and saliva begins chemical digestion. The pharynx, which plays roles in breathing and vocalization as well as digestion, runs from the nasal and oral cavities superiorly to the esophagus inferiorly (for digestion) and to the larynx anteriorly (for respiration). During deglutition (swallowing), the soft palate rises to close off the nasopharynx, the larynx elevates, and the epiglottis folds over the glottis. The esophagus includes an upper esophageal sphincter made of skeletal muscle, which regulates the movement of food from the pharynx to the esophagus. It also has a lower esophageal sphincter, made of smooth muscle, which controls the passage of food from the esophagus to the stomach. Cells in the esophageal wall secrete mucus that eases the passage of the food bolus.

## 23.4 The Stomach

The stomach participates in all digestive activities except ingestion and defecation. It vigorously churns food. It secretes gastric juices that break down food and absorb certain drugs, including aspirin and some alcohol. The stomach begins the digestion of protein and continues the digestion of carbohydrates and fats. It stores food as an acidic liquid called chyme, and releases it gradually into the small intestine through the pyloric sphincter.

## 23.5 The Small and Large Intestines

The three main regions of the small intestine are the duodenum, the jejunum, and the ileum. The small intestine is where digestion is completed and virtually all absorption occurs. These two activities are facilitated by structural adaptations that increase the mucosal surface area by 600-fold, including circular folds, villi, and microvilli. There are around 200 million microvilli per square millimeter of small intestine, which contain brush border enzymes that complete the digestion of carbohydrates and proteins. Combined with pancreatic juice, intestinal juice provides the liquid medium needed to further digest and absorb substances from chyme. The small intestine is also the site of unique mechanical digestive movements. Segmentation moves the chyme back and forth, increasing mixing and opportunities for absorption. Migrating motility complexes propel the residual chyme toward the large intestine.

The main regions of the large intestine are the cecum, the colon, and the rectum. The large intestine absorbs water and forms feces, and is responsible for defecation. Bacterial flora break down additional carbohydrate residue, and synthesize certain vitamins. The mucosa of the large intestinal wall is generously endowed with goblet cells, which secrete mucus that eases the passage of feces. The entry of feces into the rectum activates the defecation reflex.

## 23.6 Accessory Organs in Digestion: The Liver, Pancreas, and Gallbladder

Chemical digestion in the small intestine cannot occur without the help of the liver and pancreas. The liver produces bile and delivers it to the common hepatic duct. Bile contains bile salts and phospholipids, which emulsify large lipid globules into tiny lipid droplets, a necessary step in lipid digestion and absorption. The gallbladder stores and concentrates bile, releasing it when it is needed by the small intestine.

The pancreas produces the enzyme- and bicarbonate-rich pancreatic juice and delivers it to the small intestine through ducts. Pancreatic juice buffers the acidic gastric juice in chyme, inactivates pepsin from the stomach, and enables the optimal functioning of digestive enzymes in the small intestine.

## 23.7 Chemical Digestion and Absorption: A Closer Look

The small intestine is the site of most chemical digestion and almost all absorption. Chemical digestion breaks large food molecules down into their chemical building blocks, which can then be absorbed through the intestinal wall and into the general circulation. Intestinal brush border enzymes and pancreatic enzymes are responsible for the majority of chemical digestion. The breakdown of fat also requires bile.

Most nutrients are absorbed by transport mechanisms at the apical surface of enterocytes. Exceptions include lipids, fat-soluble vitamins, and most water-soluble vitamins. With the help of bile salts and lecithin, the dietary fats are emulsified to form micelles, which can carry the fat particles to the surface of the enterocytes. There, the micelles release their fats to

diffuse across the cell membrane. The fats are then reassembled into triglycerides and mixed with other lipids and proteins into chylomicrons that can pass into lacteals. Other absorbed monomers travel from blood capillaries in the villus to the hepatic portal vein and then to the liver.

## INTERACTIVE LINK QUESTIONS

- By clicking on this [link \(http://openstaxcollege.org/l/fooddigestion\)](http://openstaxcollege.org/l/fooddigestion), you can watch a short video of what happens to the food you eat as it passes from your mouth to your intestine. Along the way, note how the food changes consistency and form. How does this change in consistency facilitate your gaining nutrients from food?
- Visit this [site \(http://openstaxcollege.org/l/fooddigestion2\)](http://openstaxcollege.org/l/fooddigestion2) for an overview of digestion of food in different regions of the digestive tract. Note the route of non-fat nutrients from the small intestine to their release as nutrients to the body.
- Watch this [animation \(http://openstaxcollege.org/l/swallowing\)](http://openstaxcollege.org/l/swallowing) to see how swallowing is a complex process that involves the nervous system to coordinate the actions of upper respiratory and digestive activities. During which stage of swallowing is there a risk of food entering respiratory pathways and how is this risk blocked?
- Watch this [animation \(http://openstaxcollege.org/l/stomach1\)](http://openstaxcollege.org/l/stomach1) that depicts the structure of the stomach and how this structure functions in the initiation of protein digestion. This view of the stomach shows the characteristic rugae. What is the function of these rugae?
- Watch this [animation \(http://openstaxcollege.org/l/sintestine\)](http://openstaxcollege.org/l/sintestine) that depicts the structure of the small intestine, and, in particular, the villi. Epithelial cells continue the digestion and absorption of nutrients and transport these nutrients to the lymphatic and circulatory systems. In the small intestine, the products of food digestion are absorbed by different structures in the villi. Which structure absorbs and transports fats?
- By watching this [animation \(http://openstaxcollege.org/l/foodgroups\)](http://openstaxcollege.org/l/foodgroups), you will see that for the various food groups—proteins, fats, and carbohydrates—digestion begins in different parts of the digestion system, though all end in the same place. Of the three major food classes (carbohydrates, fats, and proteins), which is digested in the mouth, the stomach, and the small intestine?
- Watch this [video \(http://openstaxcollege.org/l/liver\)](http://openstaxcollege.org/l/liver) to see the structure of the liver and how this structure supports the functions of the liver, including the processing of nutrients, toxins, and wastes. At rest, about 1500 mL of blood per minute flow through the liver. What percentage of this blood flow comes from the hepatic portal system?

## REVIEW QUESTIONS

- Which of these organs is not considered an accessory digestive structure?
  - mouth
  - salivary glands
  - pancreas
  - liver
- Which of the following organs is supported by a layer of adventitia rather than serosa?
  - esophagus
  - stomach
  - small intestine
  - large intestine
- Which of the following membranes covers the stomach?
  - falciform ligament
  - mesocolon
  - parietal peritoneum
  - visceral peritoneum
- Which of these processes occurs in the mouth?
  - ingestion
  - mechanical digestion
  - chemical digestion
  - all of the above
- Which of these processes occurs throughout most of the alimentary canal?
  - ingestion
  - propulsion
  - segmentation
  - absorption
- Which of the following stimuli activates sensors in the walls of digestive organs?
  - breakdown products of digestion
  - distension
  - pH of chyme
  - all of the above
- Which of these statements about reflexes in the GI tract is false?
  - Short reflexes are provoked by nerves near the GI tract.
  - Short reflexes are mediated by the enteric nervous system.
  - Food that distends the stomach initiates long reflexes.
  - Long reflexes can be provoked by stimuli originating outside the GI tract.

- 15.** Which of these ingredients in saliva is responsible for activating salivary amylase?
- mucus
  - phosphate ions
  - chloride ions
  - urea
- 16.** Which of these statements about the pharynx is true?
- It extends from the nasal and oral cavities superiorly to the esophagus anteriorly.
  - The oropharynx is continuous superiorly with the nasopharynx.
  - The nasopharynx is involved in digestion.
  - The laryngopharynx is composed partially of cartilage.
- 17.** Which structure is located where the esophagus penetrates the diaphragm?
- esophageal hiatus
  - cardiac orifice
  - upper esophageal sphincter
  - lower esophageal sphincter
- 18.** Which phase of deglutition involves contraction of the longitudinal muscle layer of the muscularis?
- voluntary phase
  - buccal phase
  - pharyngeal phase
  - esophageal phase
- 19.** Which of these cells secrete hormones?
- parietal cells
  - mucous neck cells
  - enteroendocrine cells
  - chief cells
- 20.** Where does the majority of chemical digestion in the stomach occur?
- fundus and body
  - cardia and fundus
  - body and pylorus
  - body
- 21.** During gastric emptying, chyme is released into the duodenum through the \_\_\_\_\_.
- esophageal hiatus
  - pyloric antrum
  - pyloric canal
  - pyloric sphincter
- 22.** Parietal cells secrete \_\_\_\_\_.
- gastrin
  - hydrochloric acid
  - pepsin
  - pepsinogen
- 23.** In which part of the alimentary canal does most digestion occur?
- stomach
  - proximal small intestine
  - distal small intestine
  - ascending colon
- 24.** Which of these is most associated with villi?
- haustra
  - lacteals
  - bacterial flora
  - intestinal glands
- 25.** What is the role of the small intestine's MALT?
- secreting mucus
  - buffering acidic chyme
  - activating pepsin
  - preventing bacteria from entering the bloodstream
- 26.** Which part of the large intestine attaches to the appendix?
- cecum
  - ascending colon
  - transverse colon
  - descending colon
- 27.** Which of these statements about bile is true?
- About 500 mL is secreted daily.
  - Its main function is the denaturation of proteins.
  - It is synthesized in the gallbladder.
  - Bile salts are recycled.
- 28.** Pancreatic juice \_\_\_\_\_.
- deactivates bile.
  - is secreted by pancreatic islet cells.
  - buffers chyme.
  - is released into the cystic duct.
- 29.** Where does the chemical digestion of starch begin?
- mouth
  - esophagus
  - stomach
  - small intestine
- 30.** Which of these is involved in the chemical digestion of protein?
- pancreatic amylase
  - trypsin
  - sucrase
  - pancreatic nuclease
- 31.** Where are most fat-digesting enzymes produced?
- small intestine
  - gallbladder
  - liver
  - pancreas
- 32.** Which of these nutrients is absorbed mainly in the duodenum?
- glucose
  - iron
  - sodium
  - water

## CRITICAL THINKING QUESTIONS

- 33.** Explain how the enteric nervous system supports the digestive system. What might occur that could result in the autonomic nervous system having a negative impact on digestion?
- 34.** What layer of the alimentary canal tissue is capable of helping to protect the body against disease, and through what mechanism?
- 35.** Offer a theory to explain why segmentation occurs and peristalsis slows in the small intestine.
- 36.** It has been several hours since you last ate. Walking past a bakery, you catch a whiff of freshly baked bread. What type of reflex is triggered, and what is the result?
- 37.** The composition of saliva varies from gland to gland. Discuss how saliva produced by the parotid gland differs in action from saliva produced by the sublingual gland.
- 38.** During a hockey game, the puck hits a player in the mouth, knocking out all eight of his most anterior teeth. Which teeth did the player lose and how does this loss affect food ingestion?
- 39.** What prevents swallowed food from entering the airways?
- 40.** Explain the mechanism responsible for gastroesophageal reflux.
- 41.** Describe the three processes involved in the esophageal phase of deglutition.
- 42.** Explain how the stomach is protected from self-digestion and why this is necessary.
- 43.** Describe unique anatomical features that enable the stomach to perform digestive functions.
- 44.** Explain how nutrients absorbed in the small intestine pass into the general circulation.
- 45.** Why is it important that chyme from the stomach is delivered to the small intestine slowly and in small amounts?
- 46.** Describe three of the differences between the walls of the large and small intestines.
- 47.** Why does the pancreas secrete some enzymes in their inactive forms, and where are these enzymes activated?
- 48.** Describe the location of hepatocytes in the liver and how this arrangement enhances their function.
- 49.** Explain the role of bile salts and lecithin in the emulsification of lipids (fats).
- 50.** How is vitamin B<sub>12</sub> absorbed?

# 24 | METABOLISM AND NUTRITION



**Figure 24.1 Metabolism** Metabolism is the sum of all energy-requiring and energy-consuming processes of the body. Many factors contribute to overall metabolism, including lean muscle mass, the amount and quality of food consumed, and the physical demands placed on the human body. (credit: "tableatny"/flickr.com)

## Introduction

### Chapter Objectives

After studying this chapter, you will be able to:

- Describe the processes involved in anabolic and catabolic reactions
- List and describe the steps necessary for carbohydrate, lipid, and protein metabolism
- Explain the processes that regulate glucose levels during the absorptive and postabsorptive states
- Explain how metabolism is essential to maintaining body temperature (thermoregulation)
- Summarize the importance of vitamins and minerals in the diet

Eating is essential to life. Many of us look to eating as not only a necessity, but also a pleasure. You may have been told since childhood to start the day with a good breakfast to give you the energy to get through most of the day. You most likely have heard about the importance of a balanced diet, with plenty of fruits and vegetables. But what does this all mean to your body and the physiological processes it carries out each day? You need to absorb a range of nutrients so that your cells have the building blocks for metabolic processes that release the energy for the cells to carry out their daily jobs, to manufacture new proteins, cells, and body parts, and to recycle materials in the cell.

This chapter will take you through some of the chemical reactions essential to life, the sum of which is referred to as metabolism. The focus of these discussions will be anabolic reactions and catabolic reactions. You will examine the various chemical reactions that are important to sustain life, including why you must have oxygen, how mitochondria transfer energy, and the importance of certain “metabolic” hormones and vitamins.

Metabolism varies, depending on age, gender, activity level, fuel consumption, and lean body mass. Your own metabolic rate fluctuates throughout life. By modifying your diet and exercise regimen, you can increase both lean body mass and metabolic rate. Factors affecting metabolism also play important roles in controlling muscle mass. Aging is known to decrease the metabolic rate by as much as 5 percent per year. Additionally, because men tend to have more lean muscle mass than women, their basal metabolic rate (metabolic rate at rest) is higher; therefore, men tend to burn more calories than women do. Lastly, an individual’s inherent metabolic rate is a function of the proteins and enzymes derived from their genetic background. Thus, your genes play a big role in your metabolism. Nonetheless, each person’s body engages in the same overall metabolic processes.

## 24.1 | Overview of Metabolic Reactions

By the end of this section, you will be able to:

- Describe the process by which polymers are broken down into monomers
- Describe the process by which monomers are combined into polymers
- Discuss the role of ATP in metabolism
- Explain oxidation-reduction reactions
- Describe the hormones that regulate anabolic and catabolic reactions

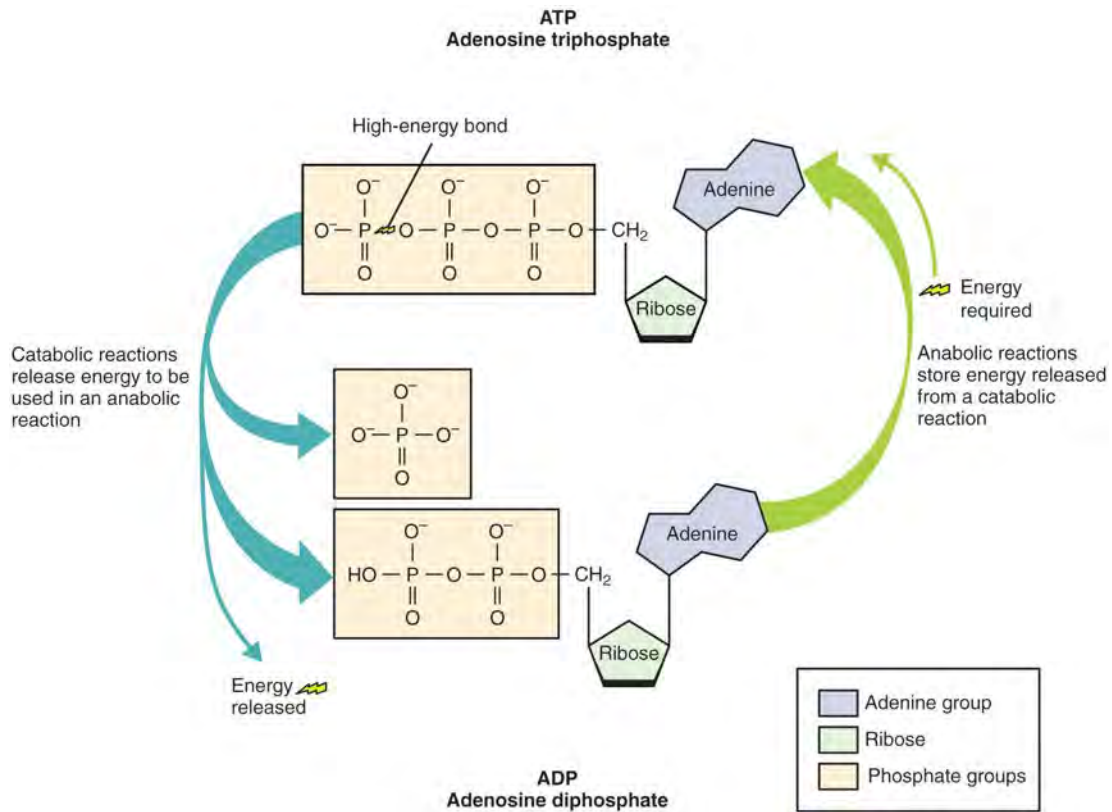
Metabolic processes are constantly taking place in the body. **Metabolism** is the sum of all of the chemical reactions that are involved in catabolism and anabolism. The reactions governing the breakdown of food to obtain energy are called catabolic reactions. Conversely, anabolic reactions use the energy produced by catabolic reactions to synthesize larger molecules from smaller ones, such as when the body forms proteins by stringing together amino acids. Both sets of reactions are critical to maintaining life.

Because catabolic reactions produce energy and anabolic reactions use energy, ideally, energy usage would balance the energy produced. If the net energy change is positive (catabolic reactions release more energy than the anabolic reactions use), then the body stores the excess energy by building fat molecules for long-term storage. On the other hand, if the net energy change is negative (catabolic reactions release less energy than anabolic reactions use), the body uses stored energy to compensate for the deficiency of energy released by catabolism.

### Catabolic Reactions

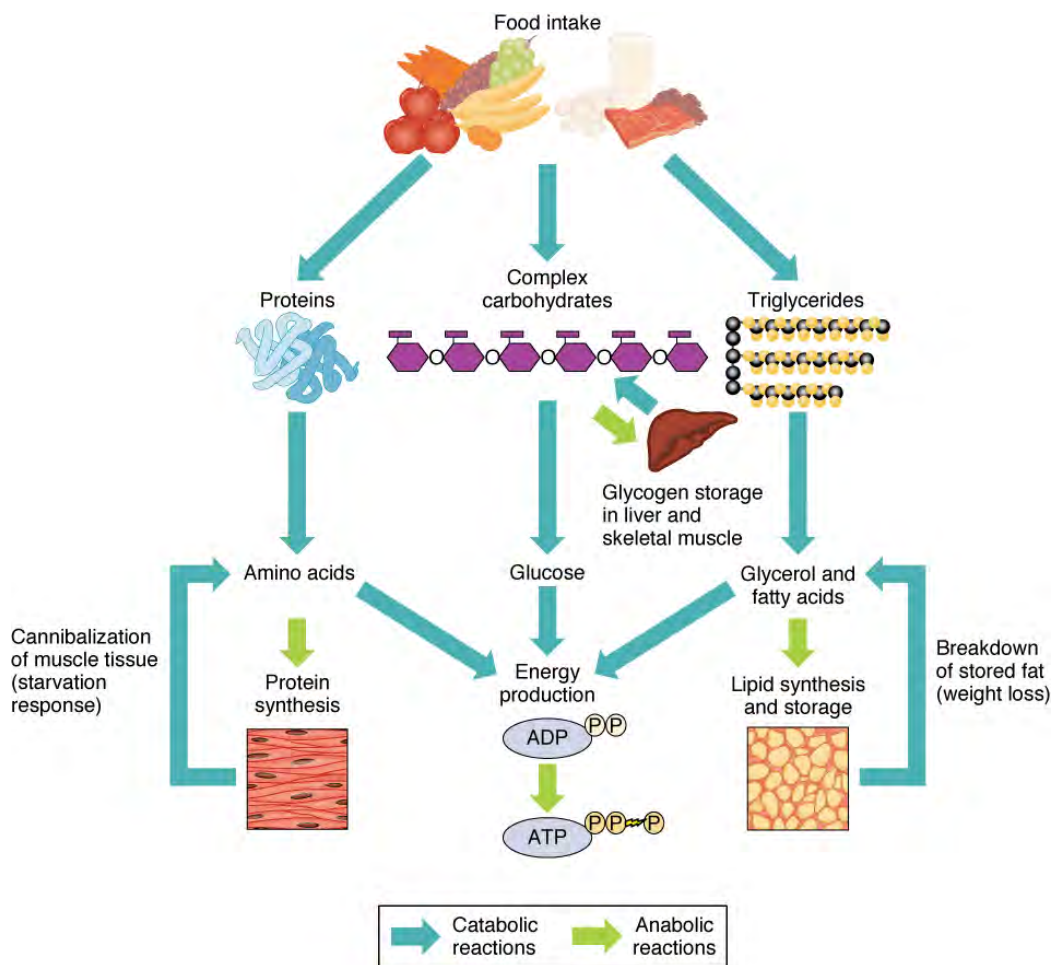
**Catabolic reactions** break down large organic molecules into smaller molecules, releasing the energy contained in the chemical bonds. These energy releases (conversions) are not 100 percent efficient. The amount of energy released is less than the total amount contained in the molecule. Approximately 40 percent of energy yielded from catabolic reactions is directly transferred to the high-energy molecule adenosine triphosphate (ATP). ATP, the energy currency of cells, can be used immediately to power molecular machines that support cell, tissue, and organ function. This includes building new tissue and repairing damaged tissue. ATP can also be stored to fulfill future energy demands. The remaining 60 percent of the energy released from catabolic reactions is given off as heat, which tissues and body fluids absorb.

Structurally, ATP molecules consist of an adenine, a ribose, and three phosphate groups (**Figure 24.2**). The chemical bond between the second and third phosphate groups, termed a high-energy bond, represents the greatest source of energy in a cell. It is the first bond that catabolic enzymes break when cells require energy to do work. The products of this reaction are a molecule of adenosine diphosphate (ADP) and a lone phosphate group ( $P_i$ ). ATP, ADP, and  $P_i$  are constantly being cycled through reactions that build ATP and store energy, and reactions that break down ATP and release energy.



**Figure 24.2 Structure of ATP Molecule** Adenosine triphosphate (ATP) is the energy molecule of the cell. During catabolic reactions, ATP is created and energy is stored until needed during anabolic reactions.

The energy from ATP drives all bodily functions, such as contracting muscles, maintaining the electrical potential of nerve cells, and absorbing food in the gastrointestinal tract. The metabolic reactions that produce ATP come from various sources (**Figure 24.3**).



**Figure 24.3 Sources of ATP** During catabolic reactions, proteins are broken down into amino acids, lipids are broken down into fatty acids, and polysaccharides are broken down into monosaccharides. These building blocks are then used for the synthesis of molecules in anabolic reactions.

Of the four major macromolecular groups (carbohydrates, lipids, proteins, and nucleic acids) that are processed by digestion, carbohydrates are considered the most common source of energy to fuel the body. They take the form of either complex carbohydrates, polysaccharides like starch and glycogen, or simple sugars (monosaccharides) like glucose and fructose. Sugar catabolism breaks polysaccharides down into their individual monosaccharides. Among the monosaccharides, glucose is the most common fuel for ATP production in cells, and as such, there are a number of endocrine control mechanisms to regulate glucose concentration in the bloodstream. Excess glucose is either stored as an energy reserve in the liver and skeletal muscles as the complex polymer glycogen, or it is converted into fat (triglyceride) in adipose cells (adipocytes).

Among the lipids (fats), triglycerides are most often used for energy via a metabolic process called  $\beta$ -oxidation. About one-half of excess fat is stored in adipocytes that accumulate in the subcutaneous tissue under the skin, whereas the rest is stored in adipocytes in other tissues and organs.

Proteins, which are polymers, can be broken down into their monomers, individual amino acids. Amino acids can be used as building blocks of new proteins or broken down further for the production of ATP. When one is chronically starving, this use of amino acids for energy production can lead to a wasting away of the body, as more and more proteins are broken down.

Nucleic acids are present in most of the foods you eat. During digestion, nucleic acids including DNA and various RNAs are broken down into their constituent nucleotides. These nucleotides are readily absorbed and transported throughout the body to be used by individual cells during nucleic acid metabolism.

## Anabolic Reactions

In contrast to catabolic reactions, **anabolic reactions** involve the joining of smaller molecules into larger ones. Anabolic reactions combine monosaccharides to form polysaccharides, fatty acids to form triglycerides, amino acids to form proteins, and nucleotides to form nucleic acids. These processes require energy in the form of ATP molecules generated by catabolic reactions. Anabolic reactions, also called **biosynthesis reactions**, create new molecules that form new cells and tissues, and revitalize organs.

## Hormonal Regulation of Metabolism

Catabolic and anabolic hormones in the body help regulate metabolic processes. **Catabolic hormones** stimulate the breakdown of molecules and the production of energy. These include cortisol, glucagon, adrenaline/epinephrine, and cytokines. All of these hormones are mobilized at specific times to meet the needs of the body. **Anabolic hormones** are required for the synthesis of molecules and include growth hormone, insulin-like growth factor, insulin, testosterone, and estrogen. **Table 24.1** summarizes the function of each of the catabolic hormones and **Table 24.2** summarizes the functions of the anabolic hormones.

### Catabolic Hormones

Hormone	Function
Cortisol	Released from the adrenal gland in response to stress; its main role is to increase blood glucose levels by gluconeogenesis (breaking down fats and proteins)
Glucagon	Released from alpha cells in the pancreas either when starving or when the body needs to generate additional energy; it stimulates the breakdown of glycogen in the liver to increase blood glucose levels; its effect is the opposite of insulin; glucagon and insulin are a part of a negative-feedback system that stabilizes blood glucose levels
Adrenaline/epinephrine	Released in response to the activation of the sympathetic nervous system; increases heart rate and heart contractility, constricts blood vessels, is a bronchodilator that opens (dilates) the bronchi of the lungs to increase air volume in the lungs, and stimulates gluconeogenesis

**Table 24.1**

### Anabolic Hormones

Hormone	Function
Growth hormone (GH)	Synthesized and released from the pituitary gland; stimulates the growth of cells, tissues, and bones
Insulin-like growth factor (IGF)	Stimulates the growth of muscle and bone while also inhibiting cell death (apoptosis)
Insulin	Produced by the beta cells of the pancreas; plays an essential role in carbohydrate and fat metabolism, controls blood glucose levels, and promotes the uptake of glucose into body cells; causes cells in muscle, adipose tissue, and liver to take up glucose from the blood and store it in the liver and muscle as glycogen; its effect is the opposite of glucagon; glucagon and insulin are a part of a negative-feedback system that stabilizes blood glucose levels
Testosterone	Produced by the testes in males and the ovaries in females; stimulates an increase in muscle mass and strength as well as the growth and strengthening of bone
Estrogen	Produced primarily by the ovaries, it is also produced by the liver and adrenal glands; its anabolic functions include increasing metabolism and fat deposition

**Table 24.2**

## Disorders OF THE...

### Metabolic Processes: Cushing Syndrome and Addison's Disease

As might be expected for a fundamental physiological process like metabolism, errors or malfunctions in metabolic processing lead to a pathophysiology or—if uncorrected—a disease state. Metabolic diseases are most commonly the result of malfunctioning proteins or enzymes that are critical to one or more metabolic pathways. Protein or enzyme malfunction can be the consequence of a genetic alteration or mutation. However, normally functioning proteins and enzymes can also have deleterious effects if their availability is not appropriately matched with metabolic need. For example, excessive production of the hormone cortisol (see **Table 24.1**) gives rise to Cushing syndrome. Clinically, Cushing syndrome is characterized by rapid weight gain, especially in the trunk and face region, depression, and anxiety. It is worth mentioning that tumors of the pituitary that produce adrenocorticotropic hormone (ACTH), which subsequently stimulates the adrenal cortex to release excessive cortisol, produce similar effects. This indirect mechanism of cortisol overproduction is referred to as Cushing disease.

Patients with Cushing syndrome can exhibit high blood glucose levels and are at an increased risk of becoming obese. They also show slow growth, accumulation of fat between the shoulders, weak muscles, bone pain (because cortisol causes proteins to be broken down to make glucose via gluconeogenesis), and fatigue. Other symptoms include excessive sweating (hyperhidrosis), capillary dilation, and thinning of the skin, which can lead to easy bruising. The treatments for Cushing syndrome are all focused on reducing excessive cortisol levels. Depending on the cause of the excess, treatment may be as simple as discontinuing the use of cortisol ointments. In cases of tumors, surgery is often used to remove the offending tumor. Where surgery is inappropriate, radiation therapy can be used to reduce the size of a tumor or ablate portions of the adrenal cortex. Finally, medications are available that can help to regulate the amounts of cortisol.

Insufficient cortisol production is equally problematic. Adrenal insufficiency, or Addison's disease, is characterized by the reduced production of cortisol from the adrenal gland. It can result from malfunction of the adrenal glands—they do not produce enough cortisol—or it can be a consequence of decreased ACTH availability from the pituitary. Patients with Addison's disease may have low blood pressure, paleness, extreme weakness, fatigue, slow or sluggish movements, lightheadedness, and salt cravings due to the loss of sodium and high blood potassium levels (hyperkalemia). Victims also may suffer from loss of appetite, chronic diarrhea, vomiting, mouth lesions, and patchy skin color. Diagnosis typically involves blood tests and imaging tests of the adrenal and pituitary glands. Treatment involves cortisol replacement therapy, which usually must be continued for life.

### Oxidation-Reduction Reactions

The chemical reactions underlying metabolism involve the transfer of electrons from one compound to another by processes catalyzed by enzymes. The electrons in these reactions commonly come from hydrogen atoms, which consist of an electron and a proton. A molecule gives up a hydrogen atom, in the form of a hydrogen ion ( $H^+$ ) and an electron, breaking the molecule into smaller parts. The loss of an electron, or **oxidation**, releases a small amount of energy; both the electron and the energy are then passed to another molecule in the process of **reduction**, or the gaining of an electron. These two reactions always happen together in an **oxidation-reduction reaction** (also called a redox reaction)—when an electron is passed between molecules, the donor is oxidized and the recipient is reduced. Oxidation-reduction reactions often happen in a series, so that a molecule that is reduced is subsequently oxidized, passing on not only the electron it just received but also the energy it received. As the series of reactions progresses, energy accumulates that is used to combine  $P_i$  and ADP to form ATP, the high-energy molecule that the body uses for fuel.

Oxidation-reduction reactions are catalyzed by enzymes that trigger the removal of hydrogen atoms. Coenzymes work with enzymes and accept hydrogen atoms. The two most common coenzymes of oxidation-reduction reactions are **nicotinamide adenine dinucleotide (NAD)** and **flavin adenine dinucleotide (FAD)**. Their respective reduced coenzymes are **NADH** and **FADH<sub>2</sub>**, which are energy-containing molecules used to transfer energy during the creation of ATP.

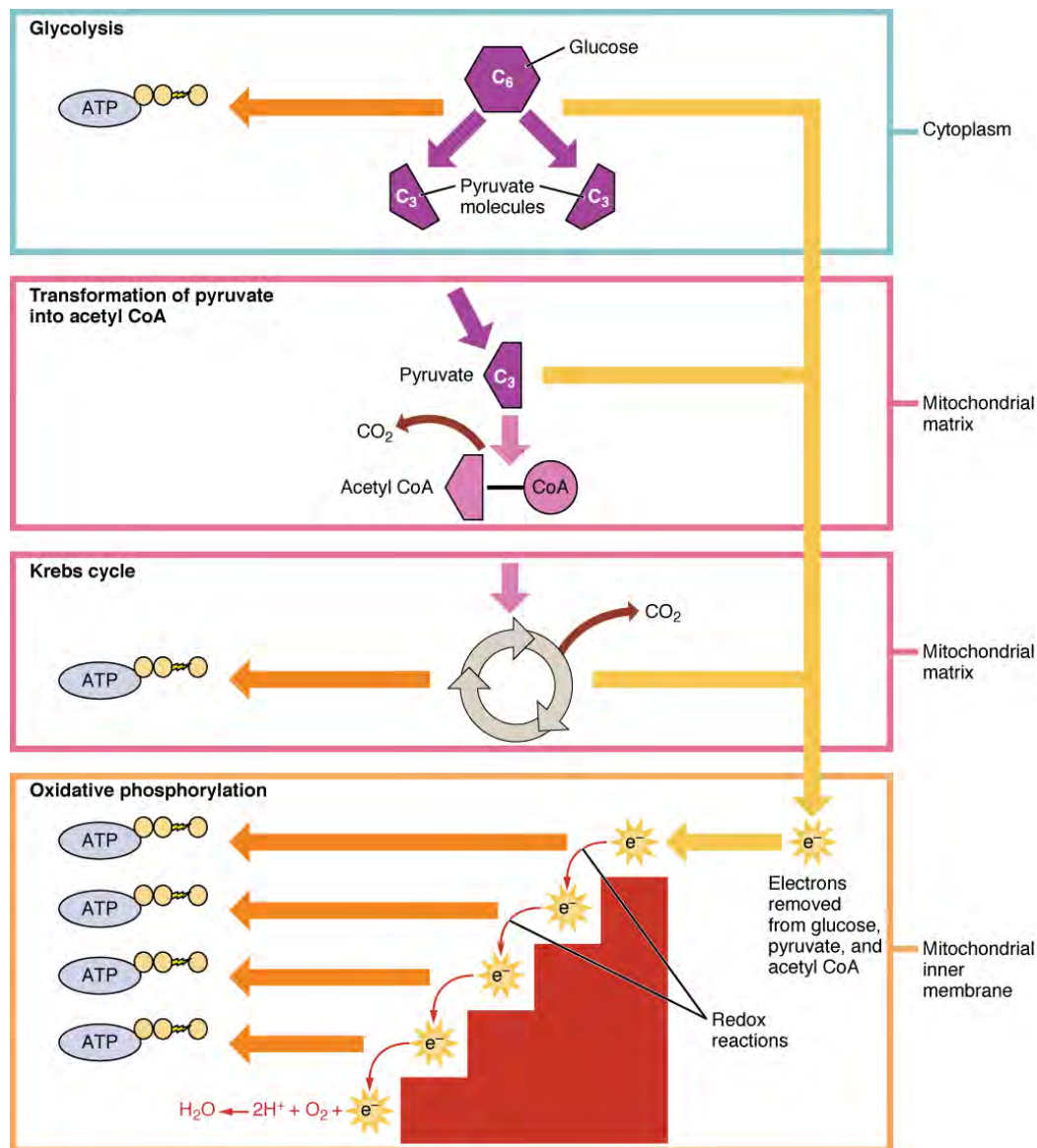
## 24.2 | Carbohydrate Metabolism

By the end of this section, you will be able to:

- Explain the processes of glycolysis
- Describe the pathway of a pyruvate molecule through the Krebs cycle
- Explain the transport of electrons through the electron transport chain
- Describe the process of ATP production through oxidative phosphorylation
- Summarize the process of gluconeogenesis

Carbohydrates are organic molecules composed of carbon, hydrogen, and oxygen atoms. The family of carbohydrates includes both simple and complex sugars. Glucose and fructose are examples of simple sugars, and starch, glycogen, and cellulose are all examples of complex sugars. The complex sugars are also called **polysaccharides** and are made of multiple **monosaccharide** molecules. Polysaccharides serve as energy storage (e.g., starch and glycogen) and as structural components (e.g., chitin in insects and cellulose in plants).

During digestion, carbohydrates are broken down into simple, soluble sugars that can be transported across the intestinal wall into the circulatory system to be transported throughout the body. Carbohydrate digestion begins in the mouth with the action of **salivary amylase** on starches and ends with monosaccharides being absorbed across the epithelium of the small intestine. Once the absorbed monosaccharides are transported to the tissues, the process of **cellular respiration** begins (**Figure 24.4**). This section will focus first on glycolysis, a process where the monosaccharide glucose is oxidized, releasing the energy stored in its bonds to produce ATP.



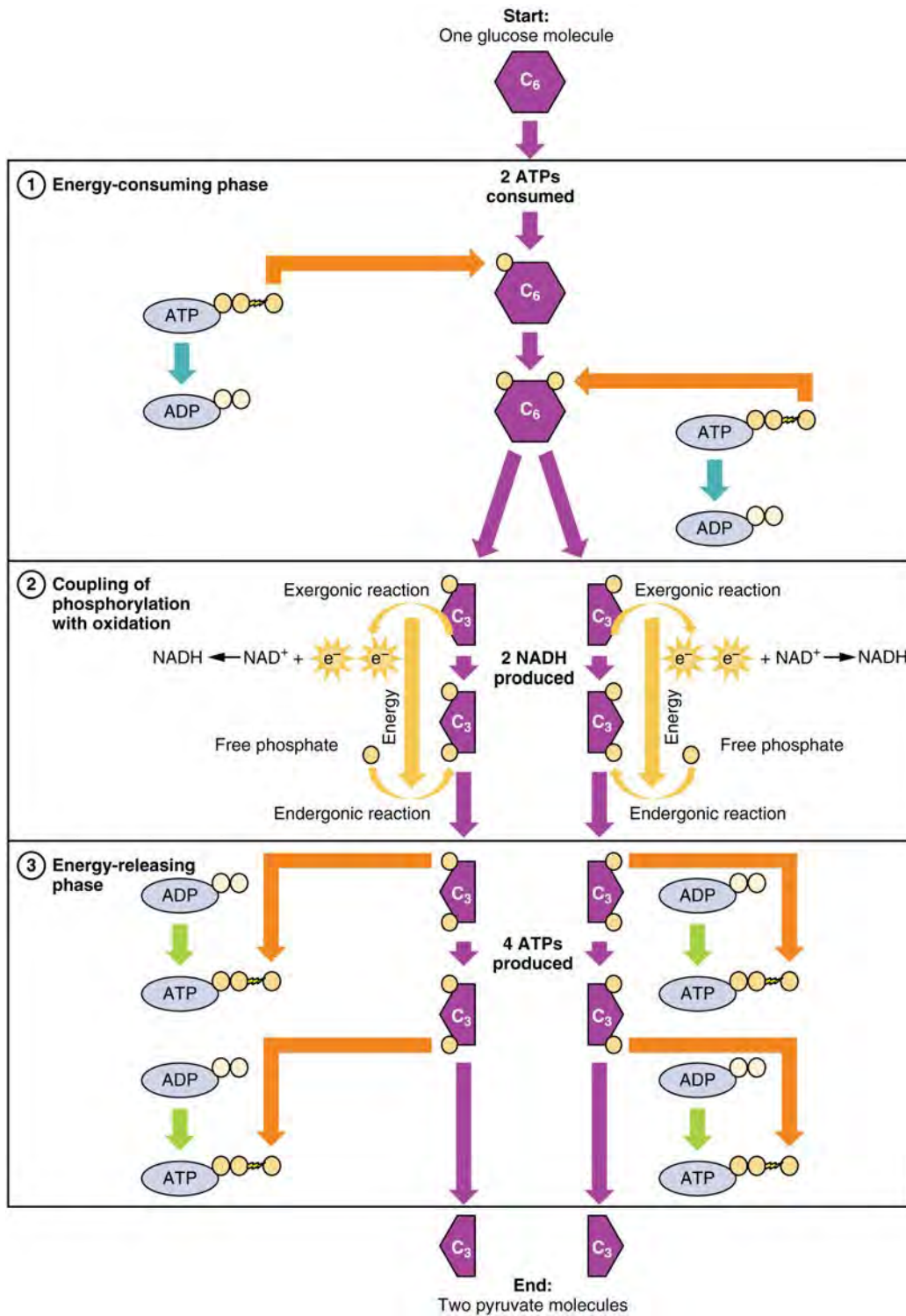
**Figure 24.4 Cellular Respiration** Cellular respiration oxidizes glucose molecules through glycolysis, the Krebs cycle, and oxidative phosphorylation to produce ATP.

## Glycolysis

Glucose is the body's most readily available source of energy. After digestive processes break polysaccharides down into monosaccharides, including glucose, the monosaccharides are transported across the wall of the small intestine and into the circulatory system, which transports them to the liver. In the liver, hepatocytes either pass the glucose on through the circulatory system or store excess glucose as glycogen. Cells in the body take up the circulating glucose in response to insulin and, through a series of reactions called **glycolysis**, transfer some of the energy in glucose to ADP to form ATP (Figure 24.5). The last step in glycolysis produces the product **pyruvate**.

Glycolysis begins with the phosphorylation of glucose by hexokinase to form glucose-6-phosphate. This step uses one ATP, which is the donor of the phosphate group. Under the action of phosphofruktokinase, glucose-6-phosphate is converted into fructose-6-phosphate. At this point, a second ATP donates its phosphate group, forming fructose-1,6-bisphosphate. This six-carbon sugar is split to form two phosphorylated three-carbon molecules, glyceraldehyde-3-phosphate and dihydroxyacetone phosphate, which are both converted into glyceraldehyde-3-phosphate. The glyceraldehyde-3-phosphate is further phosphorylated with groups donated by dihydrogen phosphate present in the cell to form the three-carbon molecule 1,3-bisphosphoglycerate. The energy of this reaction comes from the oxidation of (removal of electrons from)

glyceraldehyde-3-phosphate. In a series of reactions leading to pyruvate, the two phosphate groups are then transferred to two ADPs to form two ATPs. Thus, glycolysis uses two ATPs but generates four ATPs, yielding a net gain of two ATPs and two molecules of pyruvate. In the presence of oxygen, pyruvate continues on to the Krebs cycle (also called the **citric acid cycle** or **tricarboxylic acid cycle (TCA)**), where additional energy is extracted and passed on.



**Figure 24.5 Glycolysis Overview** During the energy-consuming phase of glycolysis, two ATPs are consumed, transferring two phosphates to the glucose molecule. The glucose molecule then splits into two three-carbon compounds, each containing a phosphate. During the second phase, an additional phosphate is added to each of the three-carbon compounds. The energy for this endergonic reaction is provided by the removal (oxidation) of two electrons from each three-carbon compound. During the energy-releasing phase, the phosphates are removed from both three-carbon compounds and used to produce four ATP molecules.

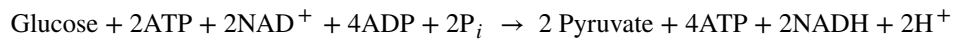
## Interactive LINK



Watch this [video \(http://openstaxcollege.org/l/glycolysis1\)](http://openstaxcollege.org/l/glycolysis1) to learn about glycolysis.

Glycolysis can be divided into two phases: energy consuming (also called chemical priming) and energy yielding. The first phase is the **energy-consuming phase**, so it requires two ATP molecules to start the reaction for each molecule of glucose. However, the end of the reaction produces four ATPs, resulting in a net gain of two ATP energy molecules.

Glycolysis can be expressed as the following equation:



This equation states that glucose, in combination with ATP (the energy source),  $\text{NAD}^+$  (a coenzyme that serves as an electron acceptor), and inorganic phosphate, breaks down into two pyruvate molecules, generating four ATP molecules—for a net yield of two ATP—and two energy-containing NADH coenzymes. The NADH that is produced in this process will be used later to produce ATP in the mitochondria. Importantly, by the end of this process, one glucose molecule generates two pyruvate molecules, two high-energy ATP molecules, and two electron-carrying NADH molecules.

The following discussions of glycolysis include the enzymes responsible for the reactions. When glucose enters a cell, the enzyme hexokinase (or glucokinase, in the liver) rapidly adds a phosphate to convert it into **glucose-6-phosphate**. A kinase is a type of enzyme that adds a phosphate molecule to a substrate (in this case, glucose, but it can be true of other molecules also). This conversion step requires one ATP and essentially traps the glucose in the cell, preventing it from passing back through the plasma membrane, thus allowing glycolysis to proceed. It also functions to maintain a concentration gradient with higher glucose levels in the blood than in the tissues. By establishing this concentration gradient, the glucose in the blood will be able to flow from an area of high concentration (the blood) into an area of low concentration (the tissues) to be either used or stored. **Hexokinase** is found in nearly every tissue in the body. **Glucokinase**, on the other hand, is expressed in tissues that are active when blood glucose levels are high, such as the liver. Hexokinase has a higher affinity for glucose than glucokinase and therefore is able to convert glucose at a faster rate than glucokinase. This is important when levels of glucose are very low in the body, as it allows glucose to travel preferentially to those tissues that require it more.

In the next step of the first phase of glycolysis, the enzyme glucose-6-phosphate isomerase converts glucose-6-phosphate into fructose-6-phosphate. Like glucose, fructose is also a six carbon-containing sugar. The enzyme phosphofructokinase-1 then adds one more phosphate to convert fructose-6-phosphate into fructose-1,6-bisphosphate, another six-carbon sugar, using another ATP molecule. Aldolase then breaks down this fructose-1,6-bisphosphate into two three-carbon molecules, glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. The triosephosphate isomerase enzyme then converts dihydroxyacetone phosphate into a second glyceraldehyde-3-phosphate molecule. Therefore, by the end of this chemical-priming or energy-consuming phase, one glucose molecule is broken down into two glyceraldehyde-3-phosphate molecules.

The second phase of glycolysis, the **energy-yielding phase**, creates the energy that is the product of glycolysis. Glyceraldehyde-3-phosphate dehydrogenase converts each three-carbon glyceraldehyde-3-phosphate produced during the energy-consuming phase into 1,3-bisphosphoglycerate. This reaction releases an electron that is then picked up by  $\text{NAD}^+$  to create an NADH molecule. NADH is a high-energy molecule, like ATP, but unlike ATP, it is not used as energy currency by the cell. Because there are two glyceraldehyde-3-phosphate molecules, two NADH molecules are synthesized during this step. Each 1,3-bisphosphoglycerate is subsequently dephosphorylated (i.e., a phosphate is removed) by phosphoglycerate kinase into 3-phosphoglycerate. Each phosphate released in this reaction can convert one molecule of ADP into one high-energy ATP molecule, resulting in a gain of two ATP molecules.

The enzyme phosphoglycerate mutase then converts the 3-phosphoglycerate molecules into 2-phosphoglycerate. The enolase enzyme then acts upon the 2-phosphoglycerate molecules to convert them into phosphoenolpyruvate molecules. The last step of glycolysis involves the dephosphorylation of the two phosphoenolpyruvate molecules by pyruvate kinase

to create two pyruvate molecules and two ATP molecules.

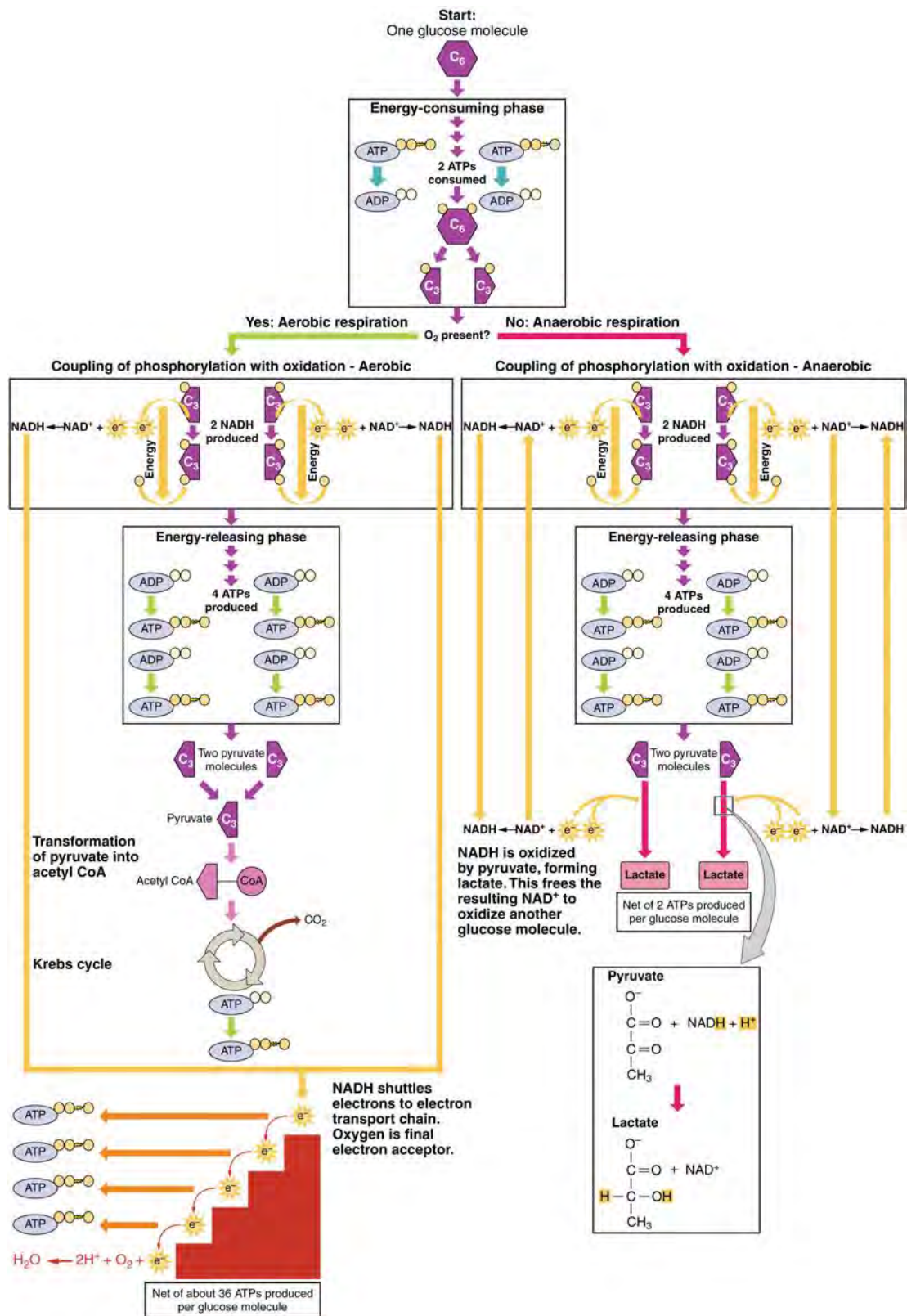
In summary, one glucose molecule breaks down into two pyruvate molecules, and creates two net ATP molecules and two NADH molecules by glycolysis. Therefore, glycolysis generates energy for the cell and creates pyruvate molecules that can be processed further through the aerobic Krebs cycle (also called the citric acid cycle or tricarboxylic acid cycle); converted into lactic acid or alcohol (in yeast) by fermentation; or used later for the synthesis of glucose through gluconeogenesis.

### Anaerobic Respiration

When oxygen is limited or absent, pyruvate enters an anaerobic pathway. In these reactions, pyruvate can be converted into lactic acid. In addition to generating an additional ATP, this pathway serves to keep the pyruvate concentration low so glycolysis continues, and it oxidizes NADH into the  $\text{NAD}^+$  needed by glycolysis. In this reaction, lactic acid replaces oxygen as the final electron acceptor. Anaerobic respiration occurs in most cells of the body when oxygen is limited or mitochondria are absent or nonfunctional. For example, because erythrocytes (red blood cells) lack mitochondria, they must produce their ATP from anaerobic respiration. This is an effective pathway of ATP production for short periods of time, ranging from seconds to a few minutes. The lactic acid produced diffuses into the plasma and is carried to the liver, where it is converted back into pyruvate or glucose via the Cori cycle. Similarly, when a person exercises, muscles use ATP faster than oxygen can be delivered to them. They depend on glycolysis and lactic acid production for rapid ATP production.

### Aerobic Respiration

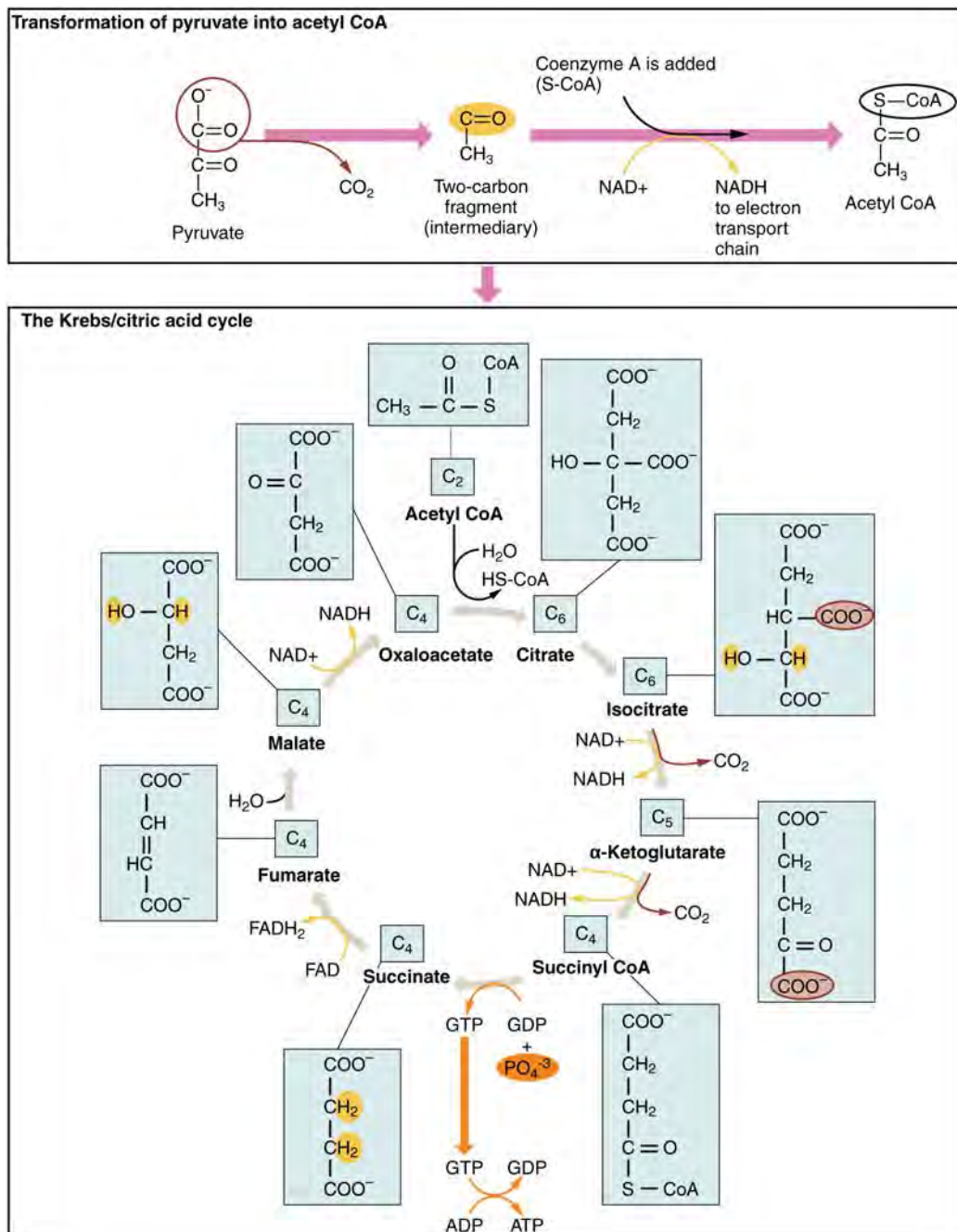
In the presence of oxygen, pyruvate can enter the Krebs cycle where additional energy is extracted as electrons are transferred from the pyruvate to the receptors  $\text{NAD}^+$ , GDP, and FAD, with carbon dioxide being a “waste product” (Figure 24.6). The NADH and  $\text{FADH}_2$  pass electrons on to the electron transport chain, which uses the transferred energy to produce ATP. As the terminal step in the electron transport chain, oxygen is the **terminal electron acceptor** and creates water inside the mitochondria.



**Figure 24.6 Aerobic versus Anaerobic Respiration** The process of anaerobic respiration converts glucose into two lactate molecules in the absence of oxygen or within erythrocytes that lack mitochondria. During aerobic respiration, glucose is oxidized into two pyruvate molecules.

## Krebs Cycle/Citric Acid Cycle/Tricarboxylic Acid Cycle

The pyruvate molecules generated during glycolysis are transported across the mitochondrial membrane into the inner mitochondrial matrix, where they are metabolized by enzymes in a pathway called the **Krebs cycle** (Figure 24.7). The Krebs cycle is also commonly called the citric acid cycle or the tricarboxylic acid (TCA) cycle. During the Krebs cycle, high-energy molecules, including ATP, NADH, and FADH<sub>2</sub>, are created. NADH and FADH<sub>2</sub> then pass electrons through the electron transport chain in the mitochondria to generate more ATP molecules.



**Figure 24.7 Krebs Cycle** During the Krebs cycle, each pyruvate that is generated by glycolysis is converted into a two-carbon acetyl CoA molecule. The acetyl CoA is systematically processed through the cycle and produces high-energy NADH, FADH<sub>2</sub>, and ATP molecules.

## Interactive LINK



Watch this **animation** (<http://openstaxcollege.org/l/krebscycle>) to observe the Krebs cycle.

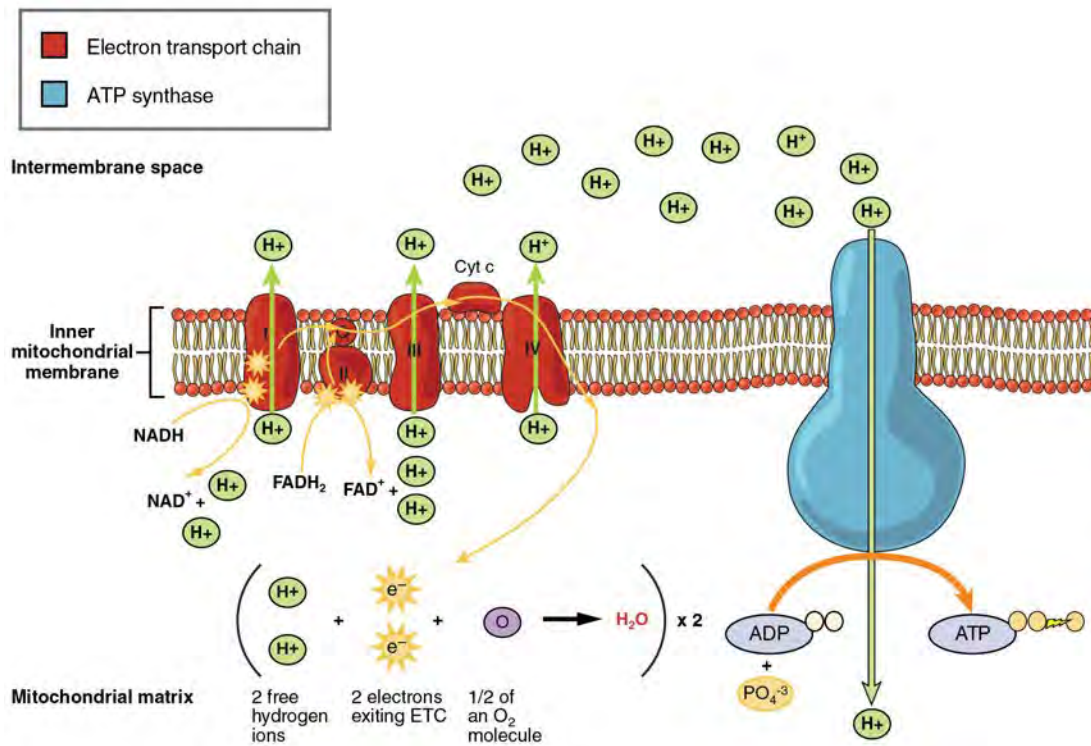
The three-carbon pyruvate molecule generated during glycolysis moves from the cytoplasm into the mitochondrial matrix, where it is converted by the enzyme pyruvate dehydrogenase into a two-carbon **acetyl coenzyme A (acetyl CoA)** molecule. This reaction is an oxidative decarboxylation reaction. It converts the three-carbon pyruvate into a two-carbon acetyl CoA molecule, releasing carbon dioxide and transferring two electrons that combine with  $\text{NAD}^+$  to form NADH. Acetyl CoA enters the Krebs cycle by combining with a four-carbon molecule, oxaloacetate, to form the six-carbon molecule citrate, or citric acid, at the same time releasing the coenzyme A molecule.

The six-carbon citrate molecule is systematically converted to a five-carbon molecule and then a four-carbon molecule, ending with oxaloacetate, the beginning of the cycle. Along the way, each citrate molecule will produce one ATP, one  $\text{FADH}_2$ , and three NADH. The  $\text{FADH}_2$  and NADH will enter the oxidative phosphorylation system located in the inner mitochondrial membrane. In addition, the Krebs cycle supplies the starting materials to process and break down proteins and fats.

To start the Krebs cycle, citrate synthase combines acetyl CoA and oxaloacetate to form a six-carbon citrate molecule; CoA is subsequently released and can combine with another pyruvate molecule to begin the cycle again. The aconitase enzyme converts citrate into isocitrate. In two successive steps of oxidative decarboxylation, two molecules of  $\text{CO}_2$  and two NADH molecules are produced when isocitrate dehydrogenase converts isocitrate into the five-carbon  $\alpha$ -ketoglutarate, which is then catalyzed and converted into the four-carbon succinyl CoA by  $\alpha$ -ketoglutarate dehydrogenase. The enzyme succinyl CoA dehydrogenase then converts succinyl CoA into succinate and forms the high-energy molecule GTP, which transfers its energy to ADP to produce ATP. Succinate dehydrogenase then converts succinate into fumarate, forming a molecule of  $\text{FADH}_2$ . Fumarase then converts fumarate into malate, which malate dehydrogenase then converts back into oxaloacetate while reducing  $\text{NAD}^+$  to NADH. Oxaloacetate is then ready to combine with the next acetyl CoA to start the Krebs cycle again (see **Figure 24.7**). For each turn of the cycle, three NADH, one ATP (through GTP), and one  $\text{FADH}_2$  are created. Each carbon of pyruvate is converted into  $\text{CO}_2$ , which is released as a byproduct of oxidative (aerobic) respiration.

## Oxidative Phosphorylation and the Electron Transport Chain

The **electron transport chain (ETC)** uses the NADH and  $\text{FADH}_2$  produced by the Krebs cycle to generate ATP. Electrons from NADH and  $\text{FADH}_2$  are transferred through protein complexes embedded in the inner mitochondrial membrane by a series of enzymatic reactions. The electron transport chain consists of a series of four enzyme complexes (Complex I – Complex IV) and two coenzymes (ubiquinone and Cytochrome c), which act as electron carriers and proton pumps used to transfer  $\text{H}^+$  ions into the space between the inner and outer mitochondrial membranes (**Figure 24.8**). The ETC couples the transfer of electrons between a donor (like NADH) and an electron acceptor (like  $\text{O}_2$ ) with the transfer of protons ( $\text{H}^+$  ions) across the inner mitochondrial membrane, enabling the process of **oxidative phosphorylation**. In the presence of oxygen, energy is passed, stepwise, through the electron carriers to collect gradually the energy needed to attach a phosphate to ADP and produce ATP. The role of molecular oxygen,  $\text{O}_2$ , is as the terminal electron acceptor for the ETC. This means that once the electrons have passed through the entire ETC, they must be passed to another, separate molecule. These electrons,  $\text{O}_2$ , and  $\text{H}^+$  ions from the matrix combine to form new water molecules. This is the basis for your need to breathe in oxygen. Without oxygen, electron flow through the ETC ceases.



**Figure 24.8 Electron Transport Chain** The electron transport chain is a series of electron carriers and ion pumps that are used to pump H<sup>+</sup> ions out of the inner mitochondrial matrix.

## Interactive LINK



Watch this [video \(http://openstaxcollege.org/l/ETchain\)](http://openstaxcollege.org/l/ETchain) to learn about the electron transport chain.

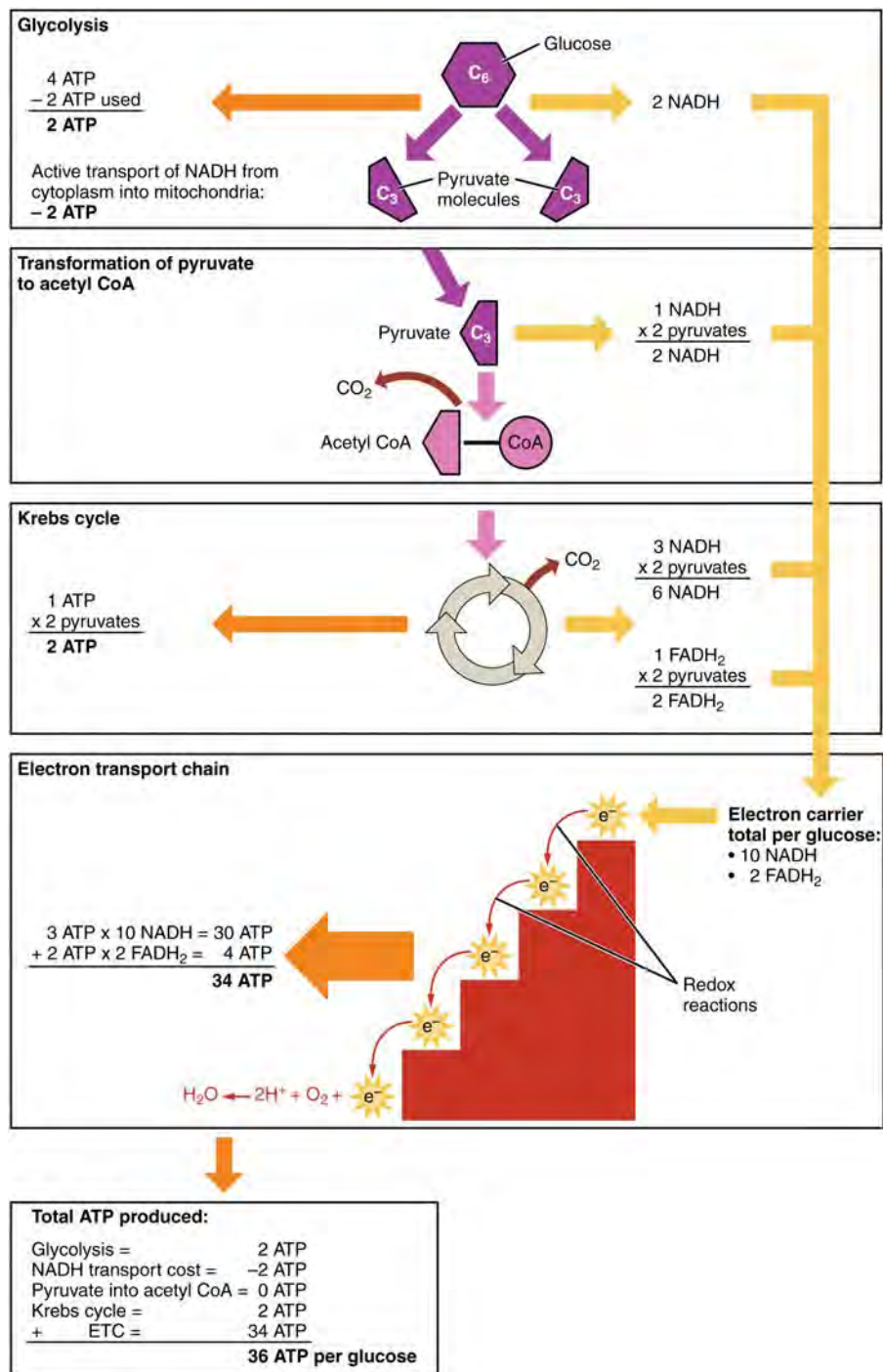
The electrons released from NADH and FADH<sub>2</sub> are passed along the chain by each of the carriers, which are reduced when they receive the electron and oxidized when passing it on to the next carrier. Each of these reactions releases a small amount of energy, which is used to pump H<sup>+</sup> ions across the inner membrane. The accumulation of these protons in the space between the membranes creates a proton gradient with respect to the mitochondrial matrix.

Also embedded in the inner mitochondrial membrane is an amazing protein pore complex called **ATP synthase**. Effectively, it is a turbine that is powered by the flow of H<sup>+</sup> ions across the inner membrane down a gradient and into the mitochondrial matrix. As the H<sup>+</sup> ions traverse the complex, the shaft of the complex rotates. This rotation enables other portions of ATP synthase to encourage ADP and P<sub>i</sub> to create ATP. In accounting for the total number of ATP produced per glucose molecule through aerobic respiration, it is important to remember the following points:

- A net of two ATP are produced through glycolysis (four produced and two consumed during the energy-consuming stage). However, these two ATP are used for transporting the NADH produced during glycolysis from the cytoplasm into the mitochondria. Therefore, the net production of ATP during glycolysis is zero.

- In all phases after glycolysis, the number of ATP, NADH, and FADH<sub>2</sub> produced must be multiplied by two to reflect how each glucose molecule produces two pyruvate molecules.
- In the ETC, about three ATP are produced for every oxidized NADH. However, only about two ATP are produced for every oxidized FADH<sub>2</sub>. The electrons from FADH<sub>2</sub> produce less ATP, because they start at a lower point in the ETC (Complex II) compared to the electrons from NADH (Complex I) (see **Figure 24.8**).

Therefore, for every glucose molecule that enters aerobic respiration, a net total of 36 ATPs are produced (**Figure 24.9**).



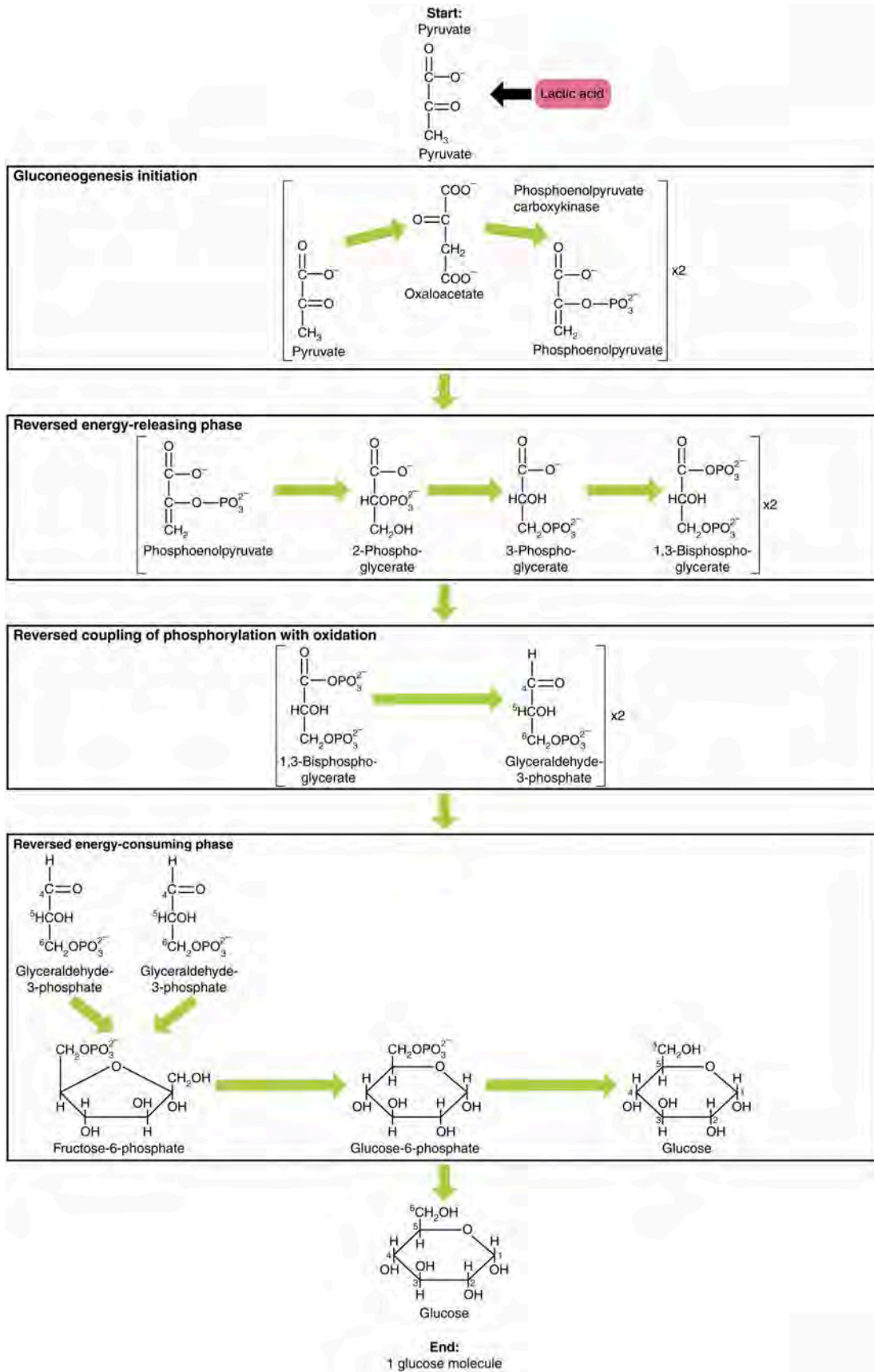
**Figure 24.9 Carbohydrate Metabolism** Carbohydrate metabolism involves glycolysis, the Krebs cycle, and the electron transport chain.

## Gluconeogenesis

**Gluconeogenesis** is the synthesis of new glucose molecules from pyruvate, lactate, glycerol, or the amino acids alanine or glutamine. This process takes place primarily in the liver during periods of low glucose, that is, under conditions of fasting, starvation, and low carbohydrate diets. So, the question can be raised as to why the body would create something it has just spent a fair amount of effort to break down? Certain key organs, including the brain, can use only glucose as an energy source; therefore, it is essential that the body maintain a minimum blood glucose concentration. When the blood glucose concentration falls below that certain point, new glucose is synthesized by the liver to raise the blood concentration to normal.

Gluconeogenesis is not simply the reverse of glycolysis. There are some important differences (**Figure 24.10**). Pyruvate is a common starting material for gluconeogenesis. First, the pyruvate is converted into oxaloacetate. Oxaloacetate then serves as a substrate for the enzyme phosphoenolpyruvate carboxykinase (PEPCK), which transforms oxaloacetate into phosphoenolpyruvate (PEP). From this step, gluconeogenesis is nearly the reverse of glycolysis. PEP is converted back into 2-phosphoglycerate, which is converted into 3-phosphoglycerate. Then, 3-phosphoglycerate is converted into 1,3 bisphosphoglycerate and then into glyceraldehyde-3-phosphate. Two molecules of glyceraldehyde-3-phosphate then combine to form fructose-1,6-bisphosphate, which is converted into fructose 6-phosphate and then into glucose-6-phosphate. Finally, a series of reactions generates glucose itself. In gluconeogenesis (as compared to glycolysis), the enzyme hexokinase is replaced by glucose-6-phosphatase, and the enzyme phosphofructokinase-1 is replaced by fructose-1,6-bisphosphatase. This helps the cell to regulate glycolysis and gluconeogenesis independently of each other.

As will be discussed as part of lipolysis, fats can be broken down into glycerol, which can be phosphorylated to form dihydroxyacetone phosphate or DHAP. DHAP can either enter the glycolytic pathway or be used by the liver as a substrate for gluconeogenesis.



**Figure 24.10 Gluconeogenesis** Gluconeogenesis is the synthesis of glucose from pyruvate, lactate, glycerol, alanine, or glutamate.

## Agng AND THE...

### Body's Metabolic Rate

The human body's metabolic rate decreases nearly 2 percent per decade after age 30. Changes in body composition, including reduced lean muscle mass, are mostly responsible for this decrease. The most dramatic loss of muscle mass, and consequential decline in metabolic rate, occurs between 50 and 70 years of age. Loss of muscle mass is the equivalent of reduced strength, which tends to inhibit seniors from engaging in sufficient physical activity. This results in a positive-feedback system where the reduced physical activity leads to even more muscle loss, further reducing metabolism.

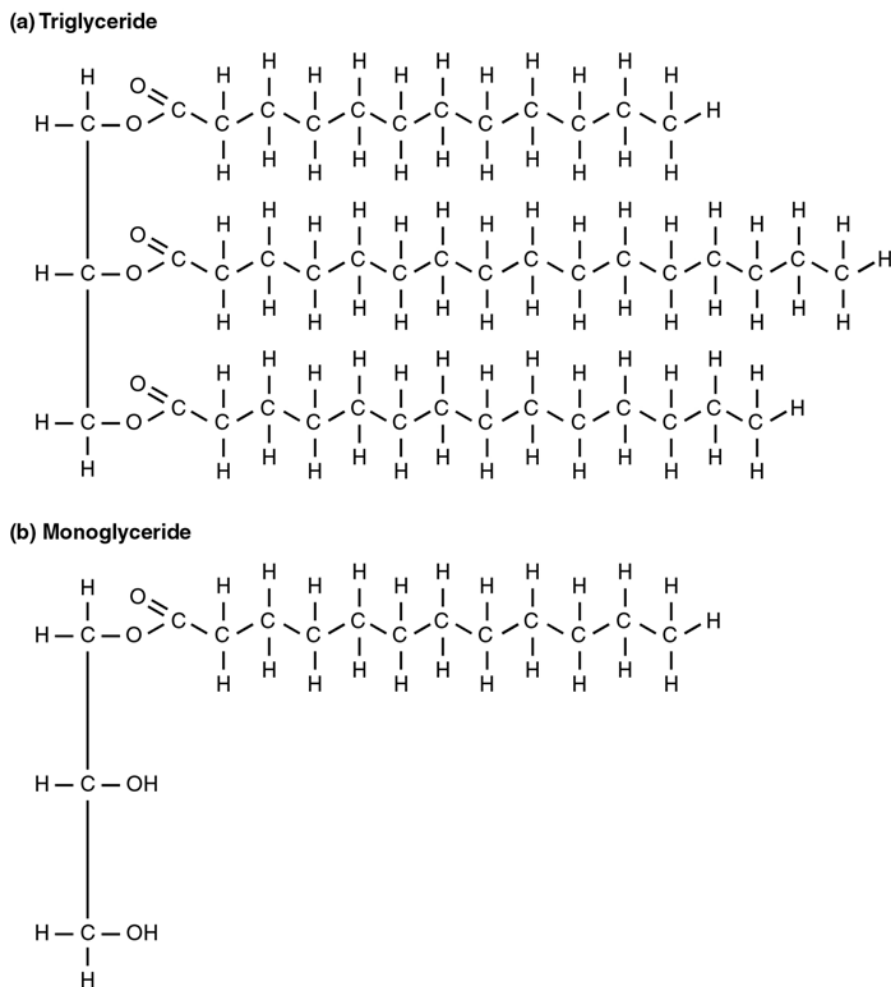
There are several things that can be done to help prevent general declines in metabolism and to fight back against the cyclic nature of these declines. These include eating breakfast, eating small meals frequently, consuming plenty of lean protein, drinking water to remain hydrated, exercising (including strength training), and getting enough sleep. These measures can help keep energy levels from dropping and curb the urge for increased calorie consumption from excessive snacking. While these strategies are not guaranteed to maintain metabolism, they do help prevent muscle loss and may increase energy levels. Some experts also suggest avoiding sugar, which can lead to excess fat storage. Spicy foods and green tea might also be beneficial. Because stress activates cortisol release, and cortisol slows metabolism, avoiding stress, or at least practicing relaxation techniques, can also help.

## 24.3 | Lipid Metabolism

By the end of this section, you will be able to:

- Explain how energy can be derived from fat
- Explain the purpose and process of ketogenesis
- Describe the process of ketone body oxidation
- Explain the purpose and the process of lipogenesis

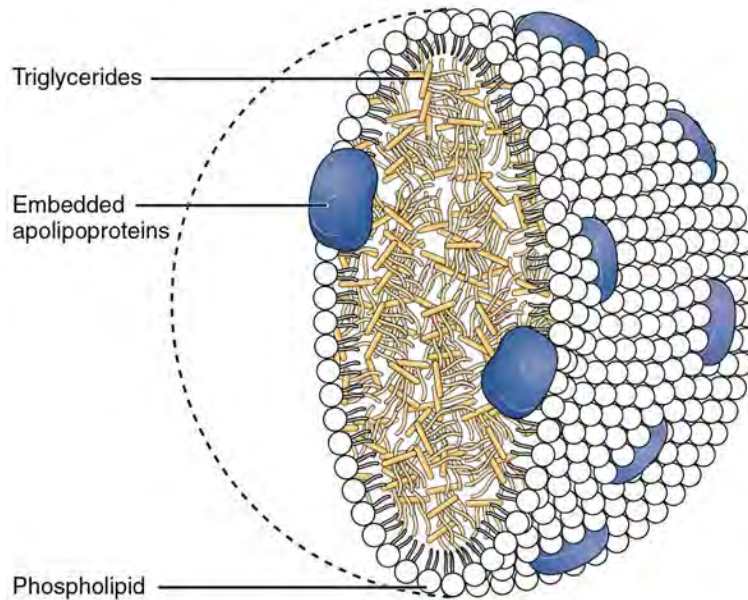
Fats (or triglycerides) within the body are ingested as food or synthesized by adipocytes or hepatocytes from carbohydrate precursors (**Figure 24.11**). Lipid metabolism entails the oxidation of fatty acids to either generate energy or synthesize new lipids from smaller constituent molecules. Lipid metabolism is associated with carbohydrate metabolism, as products of glucose (such as acetyl CoA) can be converted into lipids.



**Figure 24.11 Triglyceride Broken Down into a Monoglyceride** A triglyceride molecule (a) breaks down into a monoglyceride (b).

Lipid metabolism begins in the intestine where ingested **triglycerides** are broken down into smaller chain fatty acids and subsequently into **monoglyceride molecules** (see **Figure 24.11b**) by **pancreatic lipases**, enzymes that break down fats after they are emulsified by **bile salts**. When food reaches the small intestine in the form of chyme, a digestive hormone called **cholecystokinin (CCK)** is released by intestinal cells in the intestinal mucosa. CCK stimulates the release of pancreatic lipase from the pancreas and stimulates the contraction of the gallbladder to release stored bile salts into the intestine. CCK also travels to the brain, where it can act as a hunger suppressant.

Together, the pancreatic lipases and bile salts break down triglycerides into free fatty acids. These fatty acids can be transported across the intestinal membrane. However, once they cross the membrane, they are recombined to again form triglyceride molecules. Within the intestinal cells, these triglycerides are packaged along with cholesterol molecules in phospholipid vesicles called **chylomicrons** (**Figure 24.12**). The chylomicrons enable fats and cholesterol to move within the aqueous environment of your lymphatic and circulatory systems. Chylomicrons leave the enterocytes by exocytosis and enter the lymphatic system via lacteals in the villi of the intestine. From the lymphatic system, the chylomicrons are transported to the circulatory system. Once in the circulation, they can either go to the liver or be stored in fat cells (adipocytes) that comprise adipose (fat) tissue found throughout the body.

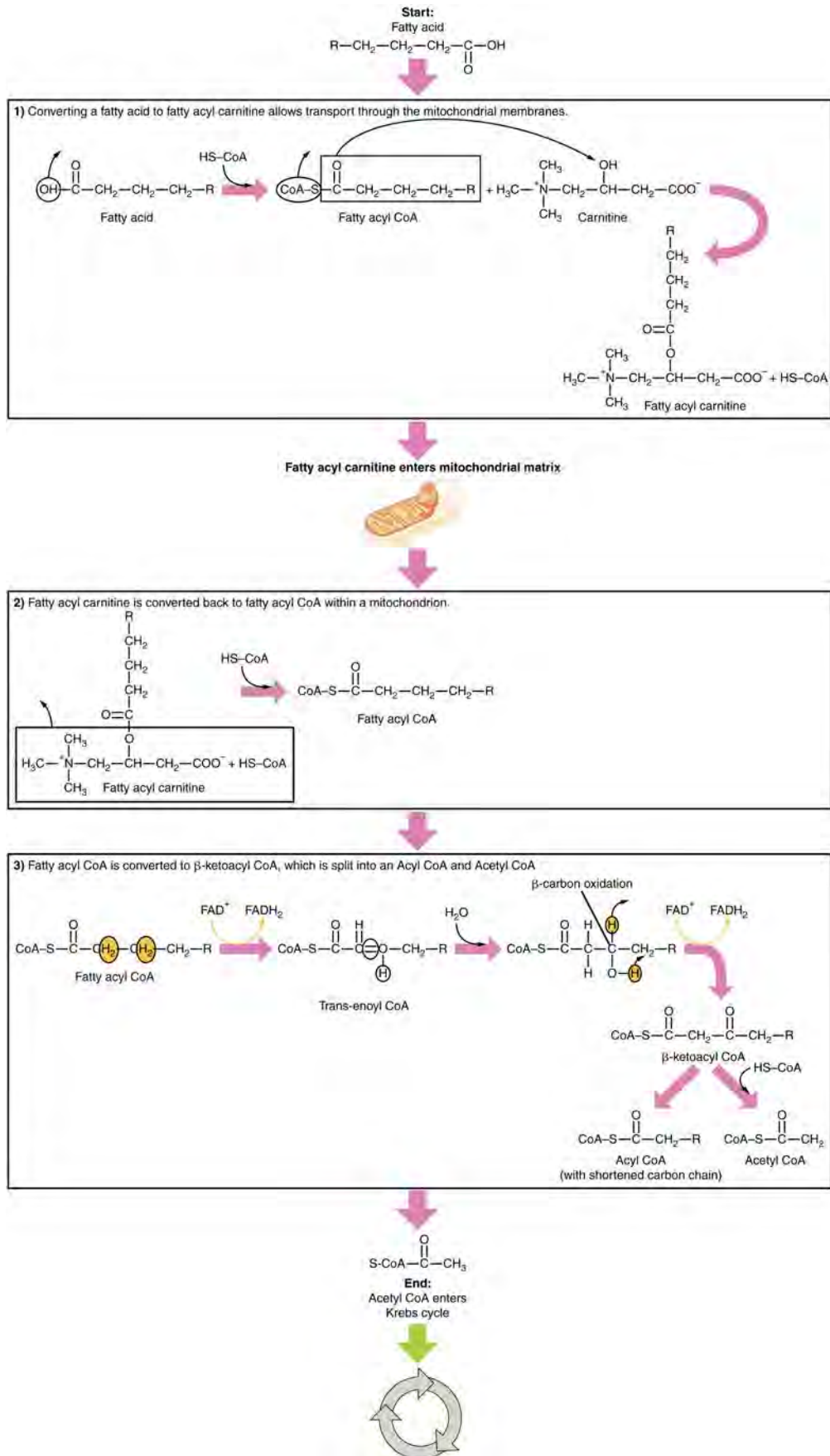


**Figure 24.12 Chylomicrons** Chylomicrons contain triglycerides, cholesterol molecules, and other apolipoproteins (protein molecules). They function to carry these water-insoluble molecules from the intestine, through the lymphatic system, and into the bloodstream, which carries the lipids to adipose tissue for storage.

## Lipolysis

To obtain energy from fat, triglycerides must first be broken down by hydrolysis into their two principal components, fatty acids and glycerol. This process, called **lipolysis**, takes place in the cytoplasm. The resulting fatty acids are oxidized by  $\beta$ -oxidation into acetyl CoA, which is used by the Krebs cycle. The glycerol that is released from triglycerides after lipolysis directly enters the glycolysis pathway as DHAP. Because one triglyceride molecule yields three fatty acid molecules with as much as 16 or more carbons in each one, fat molecules yield more energy than carbohydrates and are an important source of energy for the human body. Triglycerides yield more than twice the energy per unit mass when compared to carbohydrates and proteins. Therefore, when glucose levels are low, triglycerides can be converted into acetyl CoA molecules and used to generate ATP through aerobic respiration.

The breakdown of fatty acids, called **fatty acid oxidation** or **beta ( $\beta$ )-oxidation**, begins in the cytoplasm, where fatty acids are converted into fatty acyl CoA molecules. This fatty acyl CoA combines with carnitine to create a fatty acyl carnitine molecule, which helps to transport the fatty acid across the mitochondrial membrane. Once inside the mitochondrial matrix, the fatty acyl carnitine molecule is converted back into fatty acyl CoA and then into acetyl CoA (**Figure 24.13**). The newly formed acetyl CoA enters the Krebs cycle and is used to produce ATP in the same way as acetyl CoA derived from pyruvate.

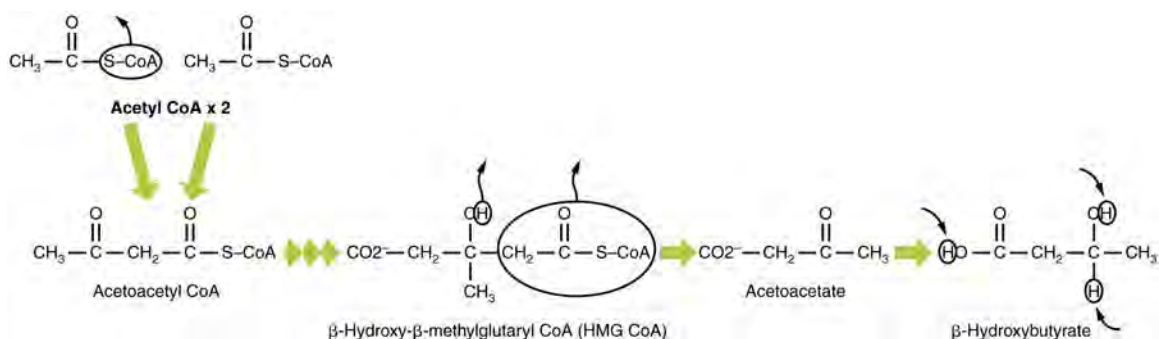


**Figure 24.13 Breakdown of Fatty Acids** During fatty acid oxidation, triglycerides can be broken down into acetyl CoA molecules and used for energy when glucose levels are low.

## Ketogenesis

If excessive acetyl CoA is created from the oxidation of fatty acids and the Krebs cycle is overloaded and cannot handle it, the acetyl CoA is diverted to create **ketone bodies**. These ketone bodies can serve as a fuel source if glucose levels are too low in the body. Ketones serve as fuel in times of prolonged starvation or when patients suffer from uncontrolled diabetes and cannot utilize most of the circulating glucose. In both cases, fat stores are liberated to generate energy through the Krebs cycle and will generate ketone bodies when too much acetyl CoA accumulates.

In this ketone synthesis reaction, excess acetyl CoA is converted into **hydroxymethylglutaryl CoA (HMG CoA)**. HMG CoA is a precursor of cholesterol and is an intermediate that is subsequently converted into  $\beta$ -hydroxybutyrate, the primary ketone body in the blood (**Figure 24.14**).

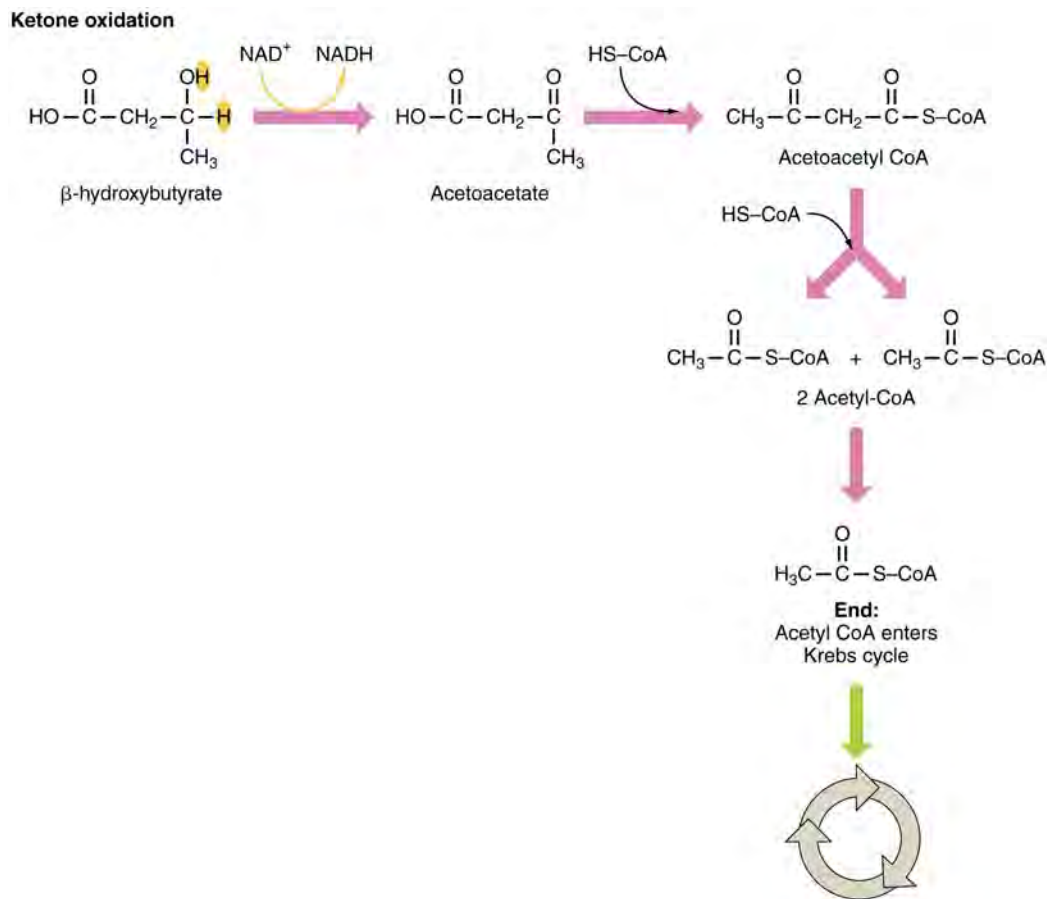


**Figure 24.14 Ketogenesis** Excess acetyl CoA is diverted from the Krebs cycle to the ketogenesis pathway. This reaction occurs in the mitochondria of liver cells. The result is the production of  $\beta$ -hydroxybutyrate, the primary ketone body found in the blood.

## Ketone Body Oxidation

Organs that have classically been thought to be dependent solely on glucose, such as the brain, can actually use ketones as an alternative energy source. This keeps the brain functioning when glucose is limited. When ketones are produced faster than they can be used, they can be broken down into  $\text{CO}_2$  and acetone. The acetone is removed by exhalation. One symptom of ketogenesis is that the patient's breath smells sweet like alcohol. This effect provides one way of telling if a diabetic is properly controlling the disease. The carbon dioxide produced can acidify the blood, leading to diabetic ketoacidosis, a dangerous condition in diabetics.

Ketones oxidize to produce energy for the brain. **beta ( $\beta$ )-hydroxybutyrate** is oxidized to acetoacetate and NADH is released. An HS-CoA molecule is added to acetoacetate, forming acetoacetyl CoA. The carbon within the acetoacetyl CoA that is not bonded to the CoA then detaches, splitting the molecule in two. This carbon then attaches to another free HS-CoA, resulting in two acetyl CoA molecules. These two acetyl CoA molecules are then processed through the Krebs cycle to generate energy (**Figure 24.15**).

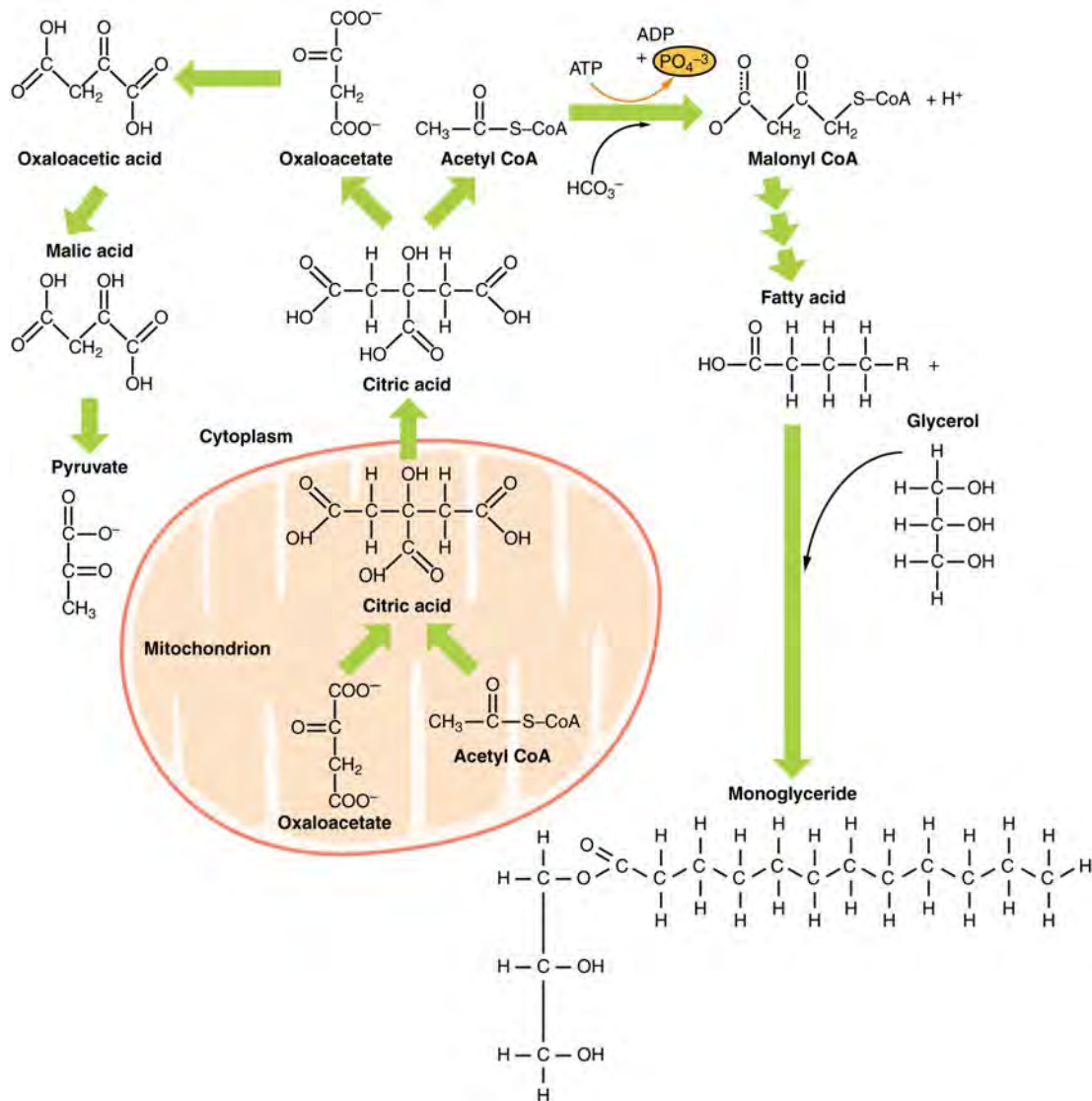


**Figure 24.15 Ketone Oxidation** When glucose is limited, ketone bodies can be oxidized to produce acetyl CoA to be used in the Krebs cycle to generate energy.

## Lipogenesis

When glucose levels are plentiful, the excess acetyl CoA generated by glycolysis can be converted into fatty acids, triglycerides, cholesterol, steroids, and bile salts. This process, called **lipogenesis**, creates lipids (fat) from the acetyl CoA and takes place in the cytoplasm of adipocytes (fat cells) and hepatocytes (liver cells). When you eat more glucose or carbohydrates than your body needs, your system uses acetyl CoA to turn the excess into fat. Although there are several metabolic sources of acetyl CoA, it is most commonly derived from glycolysis. Acetyl CoA availability is significant, because it initiates lipogenesis. Lipogenesis begins with acetyl CoA and advances by the subsequent addition of two carbon atoms from another acetyl CoA; this process is repeated until fatty acids are the appropriate length. Because this is a bond-creating anabolic process, ATP is consumed. However, the creation of triglycerides and lipids is an efficient way of storing the energy available in carbohydrates. Triglycerides and lipids, high-energy molecules, are stored in adipose tissue until they are needed.

Although lipogenesis occurs in the cytoplasm, the necessary acetyl CoA is created in the mitochondria and cannot be transported across the mitochondrial membrane. To solve this problem, pyruvate is converted into both oxaloacetate and acetyl CoA. Two different enzymes are required for these conversions. Oxaloacetate forms via the action of pyruvate carboxylase, whereas the action of pyruvate dehydrogenase creates acetyl CoA. Oxaloacetate and acetyl CoA combine to form citrate, which can cross the mitochondrial membrane and enter the cytoplasm. In the cytoplasm, citrate is converted back into oxaloacetate and acetyl CoA. Oxaloacetate is converted into malate and then into pyruvate. Pyruvate crosses back across the mitochondrial membrane to wait for the next cycle of lipogenesis. The acetyl CoA is converted into malonyl CoA that is used to synthesize fatty acids. **Figure 24.16** summarizes the pathways of lipid metabolism.



**Figure 24.16 Lipid Metabolism** Lipids may follow one of several pathways during metabolism. Glycerol and fatty acids follow different pathways.

## 24.4 | Protein Metabolism

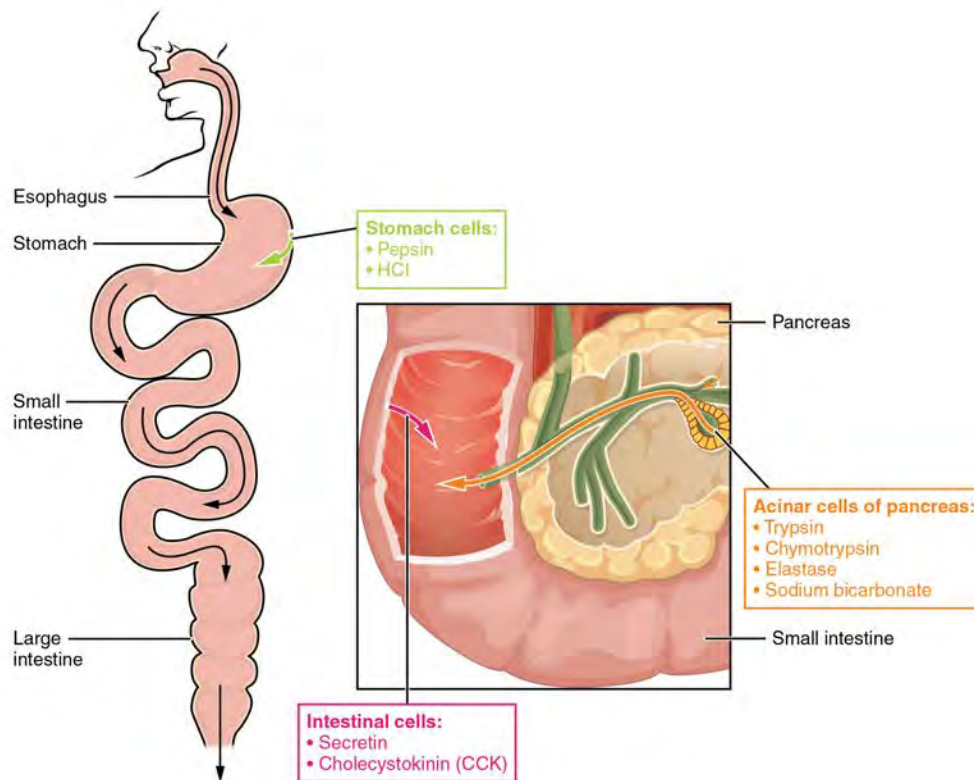
By the end of this section, you will be able to:

- Describe how the body digests proteins
- Explain how the urea cycle prevents toxic concentrations of nitrogen
- Differentiate between glucogenic and ketogenic amino acids
- Explain how protein can be used for energy

Much of the body is made of protein, and these proteins take on a myriad of forms. They represent cell signaling receptors, signaling molecules, structural members, enzymes, intracellular trafficking components, extracellular matrix scaffolds, ion pumps, ion channels, oxygen and  $\text{CO}_2$  transporters (hemoglobin). That is not even the complete list! There is protein in bones (collagen), muscles, and tendons; the hemoglobin that transports oxygen; and enzymes that catalyze all biochemical reactions. Protein is also used for growth and repair. Amid all these necessary functions, proteins also hold the potential to

serve as a metabolic fuel source. Proteins are not stored for later use, so excess proteins must be converted into glucose or triglycerides, and used to supply energy or build energy reserves. Although the body can synthesize proteins from amino acids, food is an important source of those amino acids, especially because humans cannot synthesize all of the 20 amino acids used to build proteins.

The digestion of proteins begins in the stomach. When protein-rich foods enter the stomach, they are greeted by a mixture of the enzyme **pepsin** and hydrochloric acid (HCl; 0.5 percent). The latter produces an environmental pH of 1.5–3.5 that denatures proteins within food. Pepsin cuts proteins into smaller polypeptides and their constituent amino acids. When the food-gastric juice mixture (chyme) enters the small intestine, the pancreas releases **sodium bicarbonate** to neutralize the HCl. This helps to protect the lining of the intestine. The small intestine also releases digestive hormones, including **secretin** and CCK, which stimulate digestive processes to break down the proteins further. Secretin also stimulates the pancreas to release sodium bicarbonate. The pancreas releases most of the digestive enzymes, including the proteases trypsin, chymotrypsin, and **elastase**, which aid protein digestion. Together, all of these enzymes break complex proteins into smaller individual amino acids (**Figure 24.17**), which are then transported across the intestinal mucosa to be used to create new proteins, or to be converted into fats or acetyl CoA and used in the Krebs cycle.



**Figure 24.17 Digestive Enzymes and Hormones** Enzymes in the stomach and small intestine break down proteins into amino acids. HCl in the stomach aids in proteolysis, and hormones secreted by intestinal cells direct the digestive processes.

In order to avoid breaking down the proteins that make up the pancreas and small intestine, pancreatic enzymes are released as **inactive proenzymes** that are only activated in the small intestine. In the pancreas, vesicles store **trypsin** and **chymotrypsin** as **trypsinogen** and **chymotrypsinogen**. Once released into the small intestine, an enzyme found in the wall of the small intestine, called **enterokinase**, binds to trypsinogen and converts it into its active form, trypsin. Trypsin then binds to chymotrypsinogen to convert it into the active chymotrypsin. Trypsin and chymotrypsin break down large proteins into smaller peptides, a process called **proteolysis**. These smaller peptides are catabolized into their constituent amino acids, which are transported across the apical surface of the intestinal mucosa in a process that is mediated by sodium-amino acid transporters. These transporters bind sodium and then bind the amino acid to transport it across the membrane. At the basal surface of the mucosal cells, the sodium and amino acid are released. The sodium can be reused in the transporter, whereas the amino acids are transferred into the bloodstream to be transported to the liver and cells throughout the body for protein synthesis.

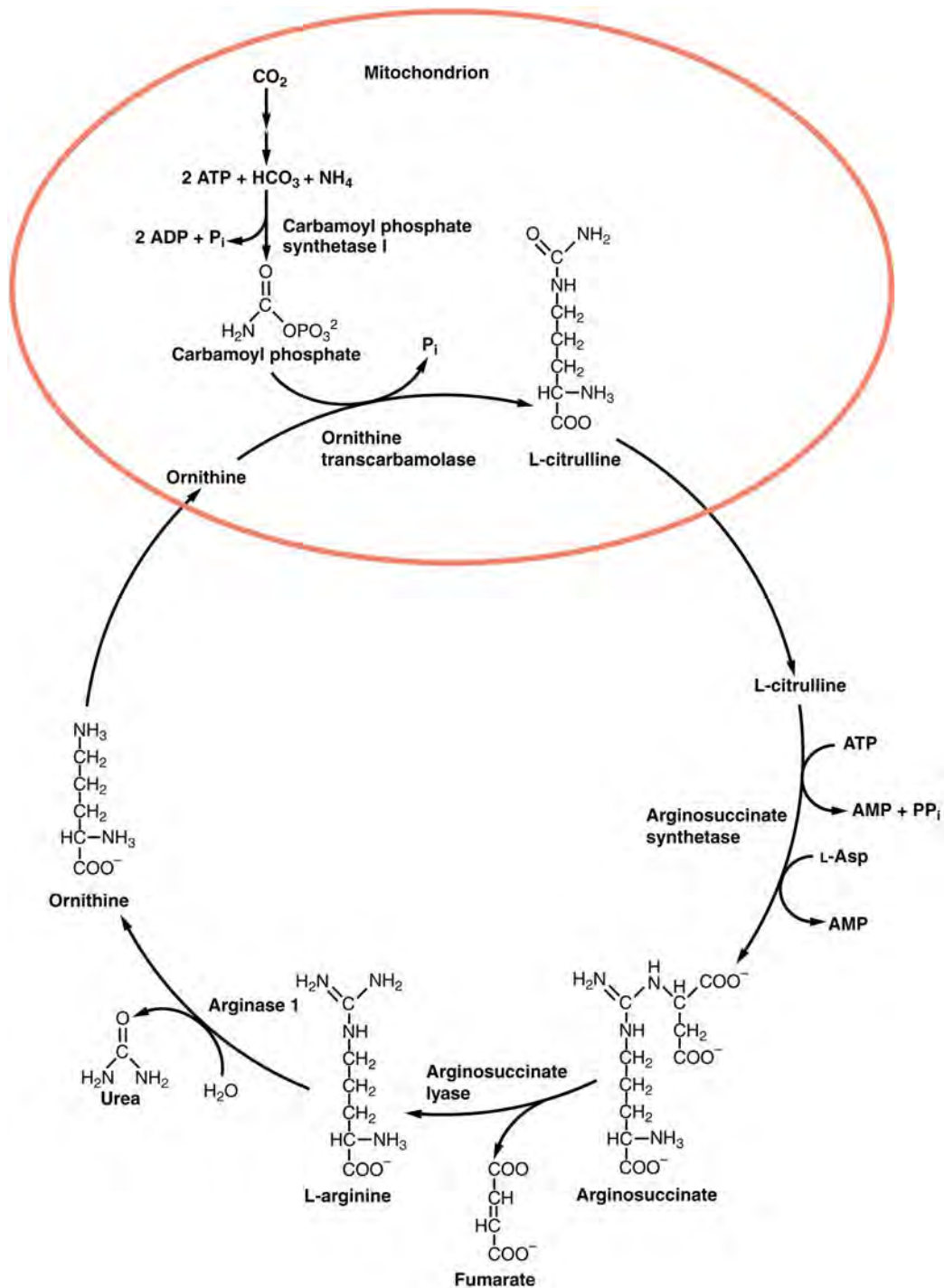
Freely available amino acids are used to create proteins. If amino acids exist in excess, the body has no capacity or

mechanism for their storage; thus, they are converted into glucose or ketones, or they are decomposed. Amino acid decomposition results in hydrocarbons and nitrogenous waste. However, high concentrations of nitrogen are toxic. The urea cycle processes nitrogen and facilitates its excretion from the body.

## Urea Cycle

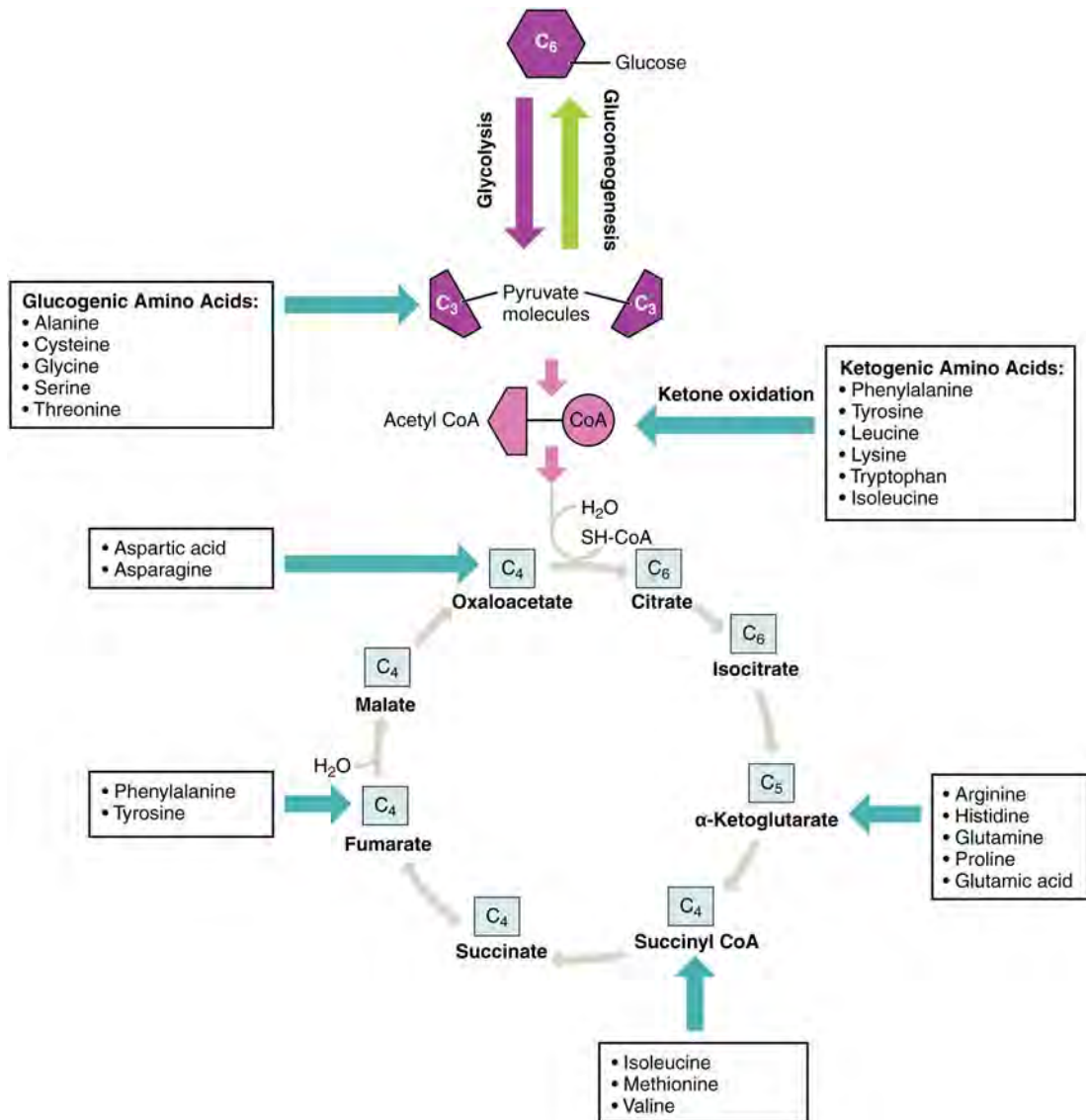
The **urea cycle** is a set of biochemical reactions that produces urea from ammonium ions in order to prevent a toxic level of ammonium in the body. It occurs primarily in the liver and, to a lesser extent, in the kidney. Prior to the urea cycle, ammonium ions are produced from the breakdown of amino acids. In these reactions, an amine group, or ammonium ion, from the amino acid is exchanged with a keto group on another molecule. This **transamination** event creates a molecule that is necessary for the Krebs cycle and an ammonium ion that enters into the urea cycle to be eliminated.

In the urea cycle, ammonium is combined with  $\text{CO}_2$ , resulting in urea and water. The urea is eliminated through the kidneys in the urine (**Figure 24.18**).

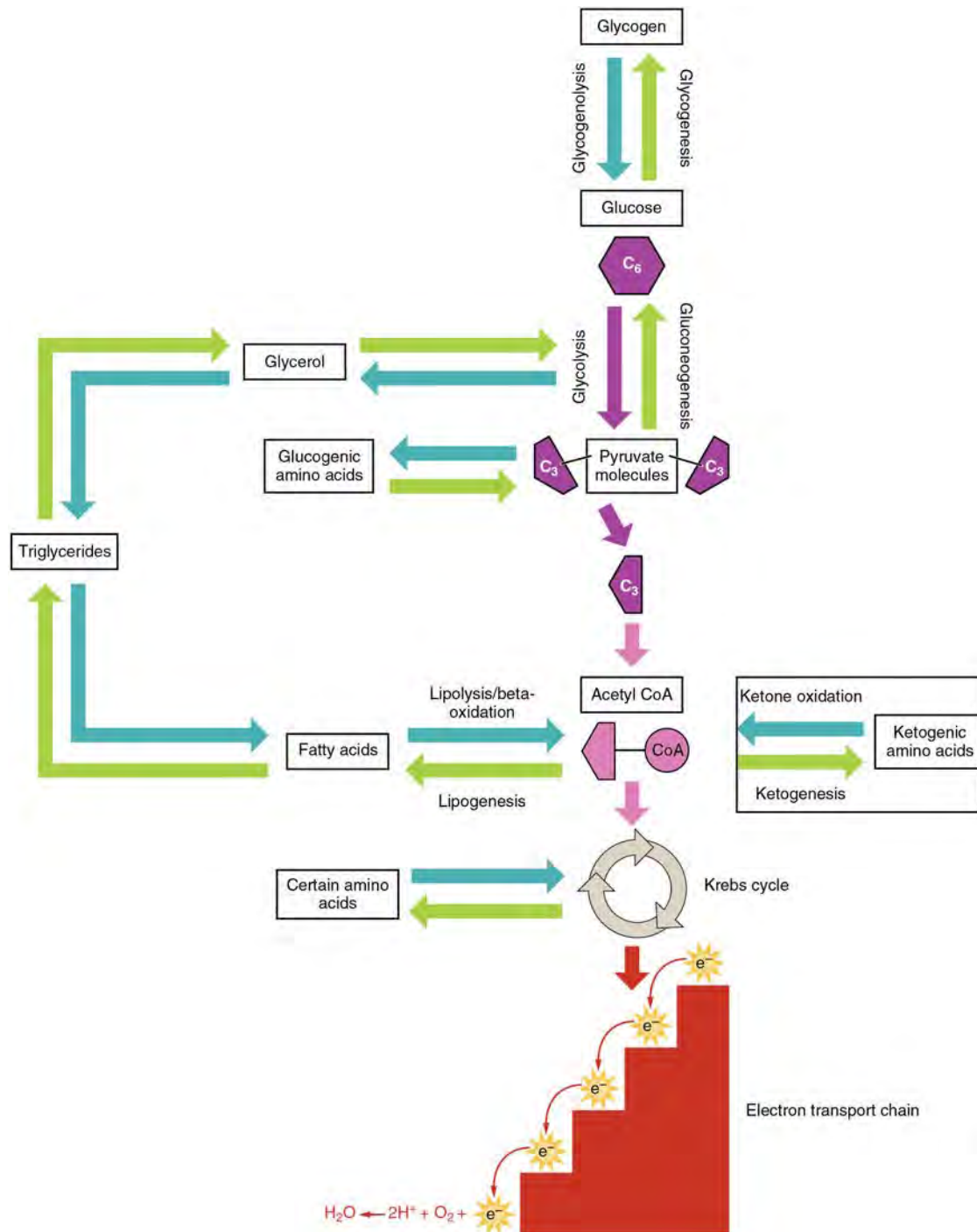


**Figure 24.18 Urea Cycle** Nitrogen is transaminated, creating ammonia and intermediates of the Krebs cycle. Ammonia is processed in the urea cycle to produce urea that is eliminated through the kidneys.

Amino acids can also be used as a source of energy, especially in times of starvation. Because the processing of amino acids results in the creation of metabolic intermediates, including pyruvate, acetyl CoA, acetoacetyl CoA, oxaloacetate, and  $\alpha$ -ketoglutarate, amino acids can serve as a source of energy production through the Krebs cycle (Figure 24.19). Figure 24.20 summarizes the pathways of catabolism and anabolism for carbohydrates, lipids, and proteins.



**Figure 24.19 Energy from Amino Acids** Amino acids can be broken down into precursors for glycolysis or the Krebs cycle. Amino acids (in bold) can enter the cycle through more than one pathway.



**Figure 24.20 Catabolic and Anabolic Pathways** Nutrients follow a complex pathway from ingestion through anabolism and catabolism to energy production.

## Disorders OF THE...

### Metabolism: Pyruvate Dehydrogenase Complex Deficiency and Phenylketonuria

Pyruvate dehydrogenase complex deficiency (PDCD) and phenylketonuria (PKU) are genetic disorders. Pyruvate dehydrogenase is the enzyme that converts pyruvate into acetyl CoA, the molecule necessary to begin the Krebs cycle to produce ATP. With low levels of the pyruvate dehydrogenase complex (PDC), the rate of cycling through the Krebs cycle is dramatically reduced. This results in a decrease in the total amount of energy that is produced by the cells of the body. PDC deficiency results in a neurodegenerative disease that ranges in severity, depending on the levels of the PDC enzyme. It may cause developmental defects, muscle spasms, and death. Treatments can include diet modification, vitamin supplementation, and gene therapy; however, damage to the central nervous system usually cannot be reversed.

PKU affects about 1 in every 15,000 births in the United States. People afflicted with PKU lack sufficient activity of the enzyme phenylalanine hydroxylase and are therefore unable to break down phenylalanine into tyrosine adequately. Because of this, levels of phenylalanine rise to toxic levels in the body, which results in damage to the central nervous system and brain. Symptoms include delayed neurological development, hyperactivity, mental retardation, seizures, skin rash, tremors, and uncontrolled movements of the arms and legs. Pregnant women with PKU are at a high risk for exposing the fetus to too much phenylalanine, which can cross the placenta and affect fetal development. Babies exposed to excess phenylalanine in utero may present with heart defects, physical and/or mental retardation, and microcephaly. Every infant in the United States and Canada is tested at birth to determine whether PKU is present. The earlier a modified diet is begun, the less severe the symptoms will be. The person must closely follow a strict diet that is low in phenylalanine to avoid symptoms and damage. Phenylalanine is found in high concentrations in artificial sweeteners, including aspartame. Therefore, these sweeteners must be avoided. Some animal products and certain starches are also high in phenylalanine, and intake of these foods should be carefully monitored.

## 24.5 | Metabolic States of the Body

By the end of this section, you will be able to:

- Describe what defines each of the three metabolic states
- Describe the processes that occur during the absorptive state of metabolism
- Describe the processes that occur during the postabsorptive state of metabolism
- Explain how the body processes glucose when the body is starved of fuel

You eat periodically throughout the day; however, your organs, especially the brain, need a continuous supply of glucose. How does the body meet this constant demand for energy? Your body processes the food you eat both to use immediately and, importantly, to store as energy for later demands. If there were no method in place to store excess energy, you would need to eat constantly in order to meet energy demands. Distinct mechanisms are in place to facilitate energy storage, and to make stored energy available during times of fasting and starvation.

### The Absorptive State

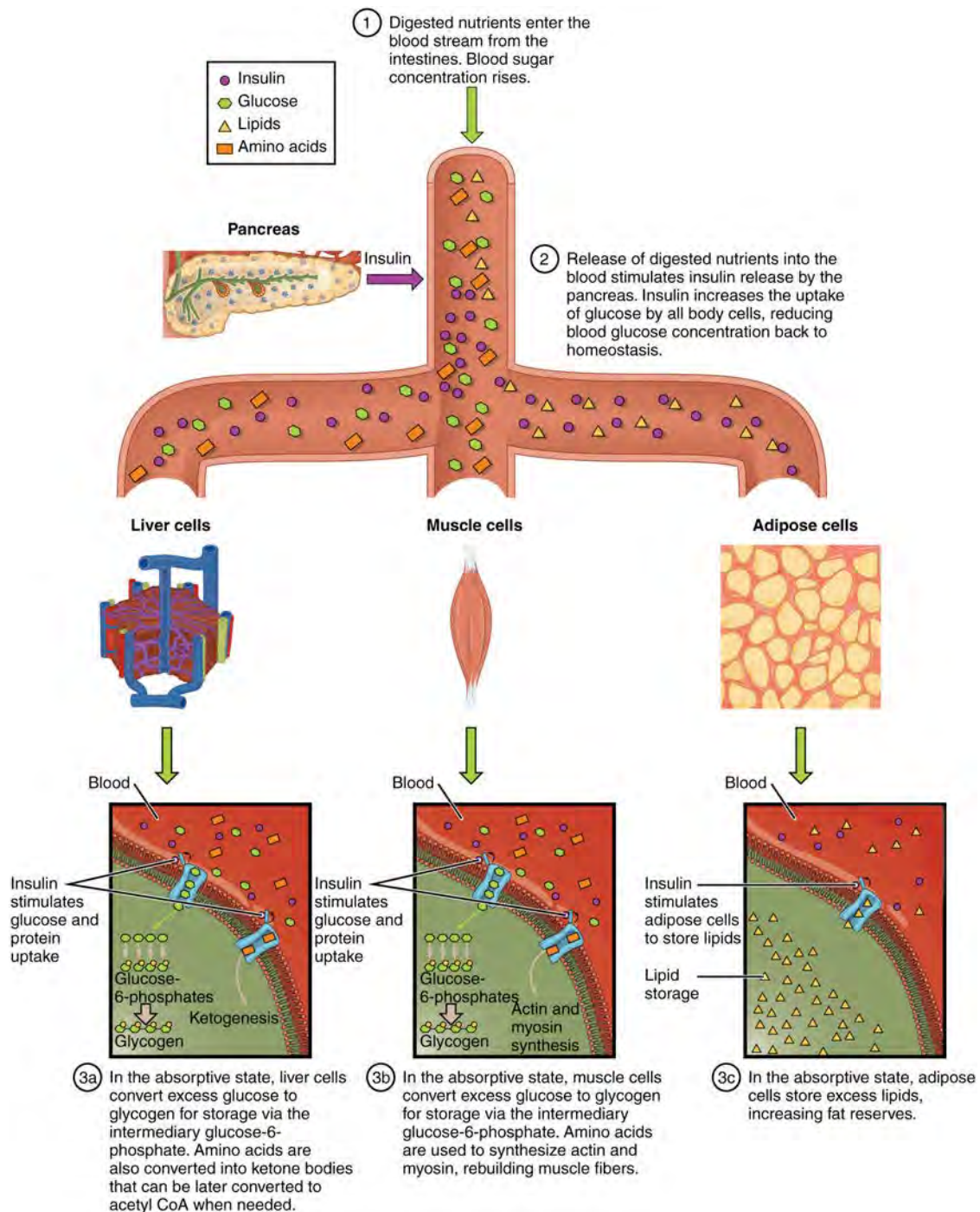
The **absorptive state**, or the fed state, occurs after a meal when your body is digesting the food and absorbing the nutrients (anabolism exceeds catabolism). Digestion begins the moment you put food into your mouth, as the food is broken down into its constituent parts to be absorbed through the intestine. The digestion of carbohydrates begins in the mouth, whereas the digestion of proteins and fats begins in the stomach and small intestine. The constituent parts of these carbohydrates, fats, and proteins are transported across the intestinal wall and enter the bloodstream (sugars and amino acids) or the lymphatic system (fats). From the intestines, these systems transport them to the liver, adipose tissue, or muscle cells that will process and use, or store, the energy.

Depending on the amounts and types of nutrients ingested, the absorptive state can linger for up to 4 hours. The ingestion of food and the rise of glucose concentrations in the bloodstream stimulate pancreatic beta cells to release **insulin** into the bloodstream, where it initiates the absorption of blood glucose by liver hepatocytes, and by adipose and muscle cells. Once

inside these cells, glucose is immediately converted into glucose-6-phosphate. By doing this, a concentration gradient is established where glucose levels are higher in the blood than in the cells. This allows for glucose to continue moving from the blood to the cells where it is needed. Insulin also stimulates the storage of glucose as glycogen in the liver and muscle cells where it can be used for later energy needs of the body. Insulin also promotes the synthesis of protein in muscle. As you will see, muscle protein can be catabolized and used as fuel in times of starvation.

If energy is exerted shortly after eating, the dietary fats and sugars that were just ingested will be processed and used immediately for energy. If not, the excess glucose is stored as glycogen in the liver and muscle cells, or as fat in adipose tissue; excess dietary fat is also stored as triglycerides in adipose tissues.

**Figure 24.21** summarizes the metabolic processes occurring in the body during the absorptive state.



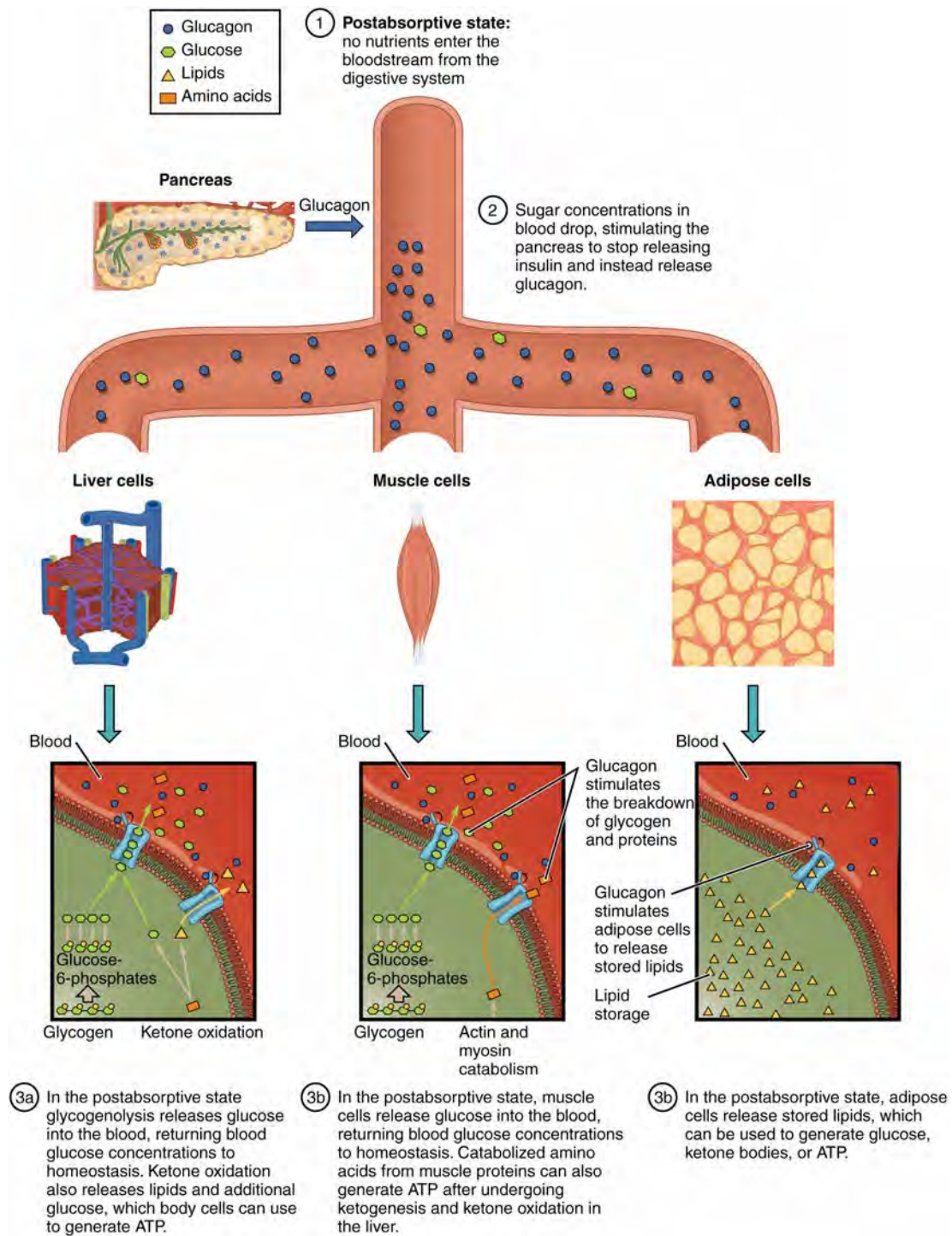
**Figure 24.21 Absorptive State** During the absorptive state, the body digests food and absorbs the nutrients.

## The Postabsorptive State

The **postabsorptive state**, or the fasting state, occurs when the food has been digested, absorbed, and stored. You commonly fast overnight, but skipping meals during the day puts your body in the postabsorptive state as well. During this state, the body must rely initially on stored **glycogen**. Glucose levels in the blood begin to drop as it is absorbed and used by the cells. In response to the decrease in glucose, insulin levels also drop. Glycogen and triglyceride storage slows. However, due to the demands of the tissues and organs, blood glucose levels must be maintained in the normal range of 80–120 mg/dL. In response to a drop in blood glucose concentration, the hormone glucagon is released from the alpha cells of the pancreas. Glucagon acts upon the liver cells, where it inhibits the synthesis of glycogen and stimulates the breakdown of

stored glycogen back into glucose. This glucose is released from the liver to be used by the peripheral tissues and the brain. As a result, blood glucose levels begin to rise. Gluconeogenesis will also begin in the liver to replace the glucose that has been used by the peripheral tissues.

After ingestion of food, fats and proteins are processed as described previously; however, the glucose processing changes a bit. The peripheral tissues preferentially absorb glucose. The liver, which normally absorbs and processes glucose, will not do so after a prolonged fast. The gluconeogenesis that has been ongoing in the liver will continue after fasting to replace the glycogen stores that were depleted in the liver. After these stores have been replenished, excess glucose that is absorbed by the liver will be converted into triglycerides and fatty acids for long-term storage. **Figure 24.22** summarizes the metabolic processes occurring in the body during the postabsorptive state.



**Figure 24.22 Postabsorptive State** During the postabsorptive state, the body must rely on stored glycogen for energy.

## Starvation

When the body is deprived of nourishment for an extended period of time, it goes into “survival mode.” The first priority for survival is to provide enough glucose or fuel for the brain. The second priority is the conservation of amino acids for proteins. Therefore, the body uses ketones to satisfy the energy needs of the brain and other glucose-dependent organs, and to maintain proteins in the cells (see [Figure 24.2](#)). Because glucose levels are very low during starvation, glycolysis will shut off in cells that can use alternative fuels. For example, muscles will switch from using glucose to fatty acids as fuel.

As previously explained, fatty acids can be converted into acetyl CoA and processed through the Krebs cycle to make ATP. Pyruvate, lactate, and alanine from muscle cells are not converted into acetyl CoA and used in the Krebs cycle, but are exported to the liver to be used in the synthesis of glucose. As starvation continues, and more glucose is needed, glycerol from fatty acids can be liberated and used as a source for gluconeogenesis.

After several days of starvation, ketone bodies become the major source of fuel for the heart and other organs. As starvation continues, fatty acids and triglyceride stores are used to create ketones for the body. This prevents the continued breakdown of proteins that serve as carbon sources for gluconeogenesis. Once these stores are fully depleted, proteins from muscles are released and broken down for glucose synthesis. Overall survival is dependent on the amount of fat and protein stored in the body.

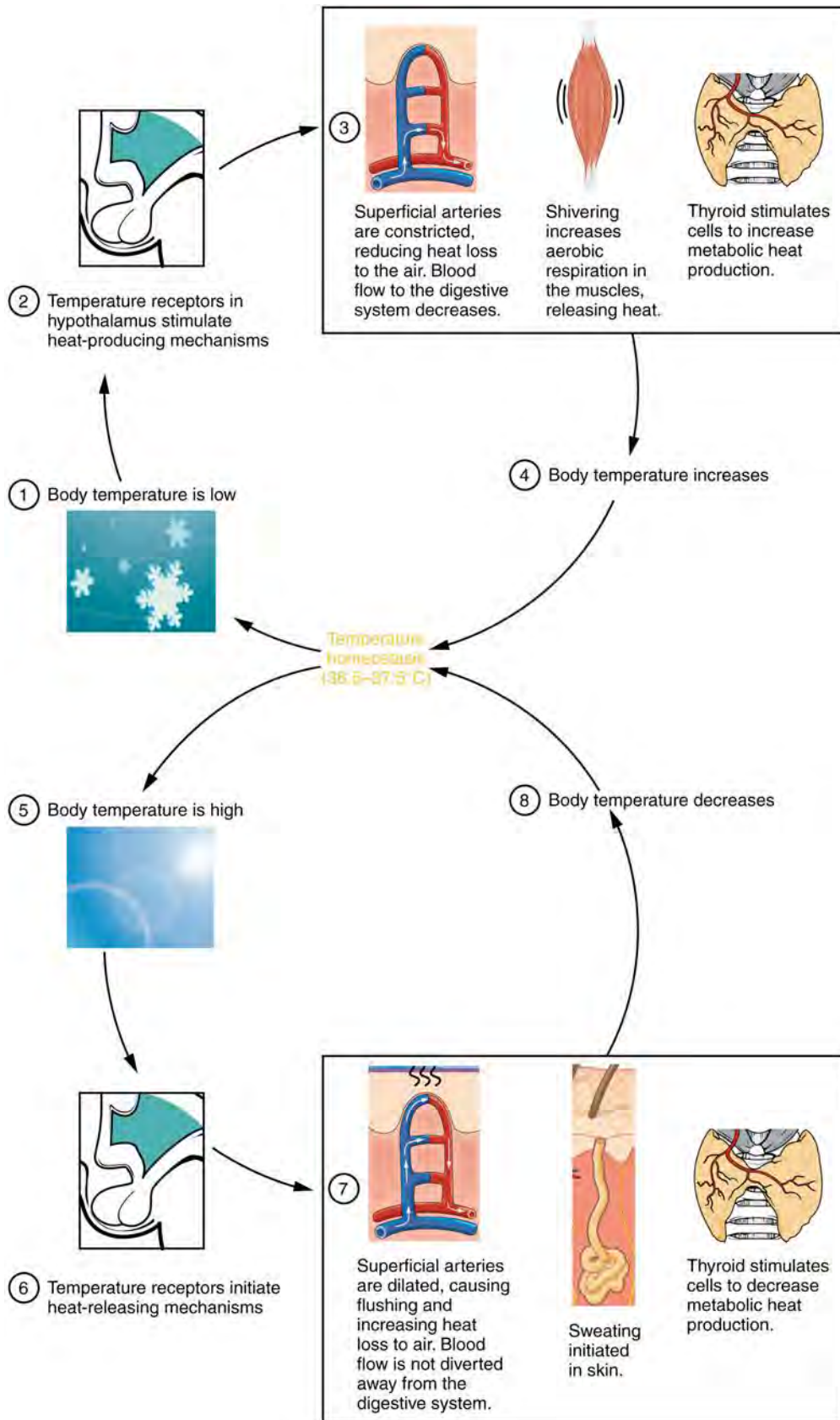
## 24.6 | Energy and Heat Balance

By the end of this section, you will be able to:

- Describe how the body regulates temperature
- Explain the significance of the metabolic rate

The body tightly regulates the body temperature through a process called **thermoregulation**, in which the body can maintain its temperature within certain boundaries, even when the surrounding temperature is very different. The core temperature of the body remains steady at around 36.5–37.5 °C (or 97.7–99.5 °F). In the process of ATP production by cells throughout the body, approximately 60 percent of the energy produced is in the form of heat used to maintain body temperature. Thermoregulation is an example of negative feedback.

The hypothalamus in the brain is the master switch that works as a thermostat to regulate the body's core temperature (**Figure 24.23**). If the temperature is too high, the hypothalamus can initiate several processes to lower it. These include increasing the circulation of the blood to the surface of the body to allow for the dissipation of heat through the skin and initiation of sweating to allow evaporation of water on the skin to cool its surface. Conversely, if the temperature falls below the set core temperature, the hypothalamus can initiate shivering to generate heat. The body uses more energy and generates more heat. In addition, thyroid hormone will stimulate more energy use and heat production by cells throughout the body. An environment is said to be **thermoneutral** when the body does not expend or release energy to maintain its core temperature. For a naked human, this is an ambient air temperature of around 84 °F. If the temperature is higher, for example, when wearing clothes, the body compensates with cooling mechanisms. The body loses heat through the mechanisms of heat exchange.



**Figure 24.23 Hypothalamus Controls Thermoregulation** The hypothalamus controls thermoregulation.

## Mechanisms of Heat Exchange

When the environment is not thermoneutral, the body uses four mechanisms of heat exchange to maintain homeostasis: conduction, convection, radiation, and evaporation. Each of these mechanisms relies on the property of heat to flow from a higher concentration to a lower concentration; therefore, each of the mechanisms of heat exchange varies in rate according to the temperature and conditions of the environment.

**Conduction** is the transfer of heat by two objects that are in direct contact with one another. It occurs when the skin comes in contact with a cold or warm object. For example, when holding a glass of ice water, the heat from your skin will warm the glass and in turn melt the ice. Alternatively, on a cold day, you might warm up by wrapping your cold hands around a hot mug of coffee. Only about 3 percent of the body's heat is lost through conduction.

**Convection** is the transfer of heat to the air surrounding the skin. The warmed air rises away from the body and is replaced by cooler air that is subsequently heated. Convection can also occur in water. When the water temperature is lower than the body's temperature, the body loses heat by warming the water closest to the skin, which moves away to be replaced by cooler water. The convection currents created by the temperature changes continue to draw heat away from the body more quickly than the body can replace it, resulting in hyperthermia. About 15 percent of the body's heat is lost through convection.

**Radiation** is the transfer of heat via infrared waves. This occurs between any two objects when their temperatures differ. A radiator can warm a room via radiant heat. On a sunny day, the radiation from the sun warms the skin. The same principle works from the body to the environment. About 60 percent of the heat lost by the body is lost through radiation.

**Evaporation** is the transfer of heat by the evaporation of water. Because it takes a great deal of energy for a water molecule to change from a liquid to a gas, evaporating water (in the form of sweat) takes with it a great deal of energy from the skin. However, the rate at which evaporation occurs depends on relative humidity—more sweat evaporates in lower humidity environments. Sweating is the primary means of cooling the body during exercise, whereas at rest, about 20 percent of the heat lost by the body occurs through evaporation.

## Metabolic Rate

The **metabolic rate** is the amount of energy consumed minus the amount of energy expended by the body. The **basal metabolic rate (BMR)** describes the amount of daily energy expended by humans at rest, in a neutrally temperate environment, while in the postabsorptive state. It measures how much energy the body needs for normal, basic, daily activity. About 70 percent of all daily energy expenditure comes from the basic functions of the organs in the body. Another 20 percent comes from physical activity, and the remaining 10 percent is necessary for body thermoregulation or temperature control. This rate will be higher if a person is more active or has more lean body mass. As you age, the BMR generally decreases as the percentage of less lean muscle mass decreases.

## 24.7 | Nutrition and Diet

By the end of this section, you will be able to:

- Explain how different foods can affect metabolism
- Describe a healthy diet, as recommended by the U.S. Department of Agriculture (USDA)
- List reasons why vitamins and minerals are critical to a healthy diet

The carbohydrates, lipids, and proteins in the foods you eat are used for energy to power molecular, cellular, and organ system activities. Importantly, the energy is stored primarily as fats. The quantity and quality of food that is ingested, digested, and absorbed affects the amount of fat that is stored as excess calories. Diet—both what you eat and how much you eat—has a dramatic impact on your health. Eating too much or too little food can lead to serious medical issues, including cardiovascular disease, cancer, anorexia, and diabetes, among others. Combine an unhealthy diet with unhealthy environmental conditions, such as smoking, and the potential medical complications increase significantly.

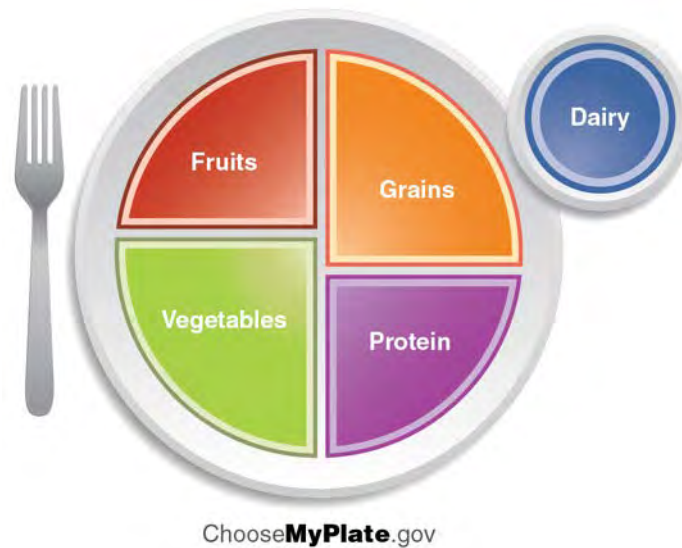
## Food and Metabolism

The amount of energy that is needed or ingested per day is measured in calories. The nutritional **Calorie (C)** is the amount of heat it takes to raise 1 kg (1000 g) of water by 1 °C. This is different from the calorie (c) used in the physical sciences, which is the amount of heat it takes to raise 1 g of water by 1 °C. When we refer to "calorie," we are referring to the nutritional Calorie.

On average, a person needs 1500 to 2000 calories per day to sustain (or carry out) daily activities. The total number of calories needed by one person is dependent on their body mass, age, height, gender, activity level, and the amount of exercise per day. If exercise is regular part of one's day, more calories are required. As a rule, people underestimate the number of calories ingested and overestimate the amount they burn through exercise. This can lead to ingestion of too many calories per day. The accumulation of an extra 3500 calories adds one pound of weight. If an excess of 200 calories per day is ingested, one extra pound of body weight will be gained every 18 days. At that rate, an extra 20 pounds can be gained over the course of a year. Of course, this increase in calories could be offset by increased exercise. Running or jogging one mile burns almost 100 calories.

The type of food ingested also affects the body's metabolic rate. Processing of carbohydrates requires less energy than processing of proteins. In fact, the breakdown of carbohydrates requires the least amount of energy, whereas the processing of proteins demands the most energy. In general, the amount of calories ingested and the amount of calories burned determines the overall weight. To lose weight, the number of calories burned per day must exceed the number ingested. Calories are in almost everything you ingest, so when considering calorie intake, beverages must also be considered.

To help provide guidelines regarding the types and quantities of food that should be eaten every day, the USDA has updated their food guidelines from MyPyramid to MyPlate. They have put the recommended elements of a healthy meal into the context of a place setting of food. MyPlate categorizes food into the standard six food groups: fruits, vegetables, grains, protein foods, dairy, and oils. The accompanying website gives clear recommendations regarding quantity and type of each food that you should consume each day, as well as identifying which foods belong in each category. The accompanying graphic (Figure 24.24) gives a clear visual with general recommendations for a healthy and balanced meal. The guidelines recommend to "Make half your plate fruits and vegetables." The other half is grains and protein, with a slightly higher quantity of grains than protein. Dairy products are represented by a drink, but the quantity can be applied to other dairy products as well.



**Figure 24.24 MyPlate** The U.S. Department of Agriculture developed food guidelines called MyPlate to help demonstrate how to maintain a healthy lifestyle.

ChooseMyPlate.gov provides extensive online resources for planning a healthy diet and lifestyle, including offering weight management tips and recommendations for physical activity. It also includes the SuperTracker, a web-based application to help you analyze your own diet and physical activity.

# Everyday CONNECTION

## Metabolism and Obesity

Obesity in the United States is epidemic. The rate of obesity has been steadily rising since the 1980s. In the 1990s, most states reported that less than 10 percent of their populations was obese, and the state with the highest rate reported that only 15 percent of their population was considered obese. By 2010, the U.S. Centers for Disease Control and Prevention reported that nearly 36 percent of adults over 20 years old were obese and an additional 33 percent were overweight, leaving only about 30 percent of the population at a healthy weight. These studies find the highest levels of obesity are concentrated in the southern states. They also find the level of childhood obesity is rising.

Obesity is defined by the **body mass index (BMI)**, which is a measure of an individual's weight-to-height ratio. The normal, or healthy, BMI range is between 18 and 24.9 kg/m<sup>2</sup>. Overweight is defined as a BMI of 25 to 29.9 kg/m<sup>2</sup>, and obesity is considered to be a BMI greater than 30 kg/m<sup>2</sup>. Obesity can arise from a number of factors, including overeating, poor diet, sedentary lifestyle, limited sleep, genetic factors, and even diseases or drugs. Severe obesity (morbid obesity) or long-term obesity can result in serious medical conditions, including coronary heart disease; type 2 diabetes; endometrial, breast, or colon cancer; hypertension (high blood pressure); dyslipidemia (high cholesterol or elevated triglycerides); stroke; liver disease; gall bladder disease; sleep apnea or respiratory diseases; osteoarthritis; and infertility. Research has shown that losing weight can help reduce or reverse the complications associated with these conditions.

## Vitamins

**Vitamins** are organic compounds found in foods and are a necessary part of the biochemical reactions in the body. They are involved in a number of processes, including mineral and bone metabolism, and cell and tissue growth, and they act as cofactors for energy metabolism. The B vitamins play the largest role of any vitamins in metabolism (**Table 24.3** and **Table 24.4**).

You get most of your vitamins through your diet, although some can be formed from the precursors absorbed during digestion. For example, the body synthesizes vitamin A from the  $\beta$ -carotene in orange vegetables like carrots and sweet potatoes. Vitamins are either fat-soluble or water-soluble. Fat-soluble vitamins A, D, E, and K, are absorbed through the intestinal tract with lipids in chylomicrons. Vitamin D is also synthesized in the skin through exposure to sunlight. Because they are carried in lipids, fat-soluble vitamins can accumulate in the lipids stored in the body. If excess vitamins are retained in the lipid stores in the body, hypervitaminosis can result.

Water-soluble vitamins, including the eight B vitamins and vitamin C, are absorbed with water in the gastrointestinal tract. These vitamins move easily through bodily fluids, which are water based, so they are not stored in the body. Excess water-soluble vitamins are excreted in the urine. Therefore, hypervitaminosis of water-soluble vitamins rarely occurs, except with an excess of vitamin supplements.

### Fat-soluble Vitamins

Vitamin and alternative name	Sources	Recommended daily allowance	Function	Problems associated with deficiency
A retinal or $\beta$ -carotene	Yellow and orange fruits and vegetables, dark green leafy vegetables, eggs, milk, liver	700–900 $\mu$ g	Eye and bone development, immune function	Night blindness, epithelial changes, immune system deficiency

**Table 24.3**

### Fat-soluble Vitamins

Vitamin and alternative name	Sources	Recommended daily allowance	Function	Problems associated with deficiency
D cholecalciferol	Dairy products, egg yolks; also synthesized in the skin from exposure to sunlight	5–15 $\mu$ g	Aids in calcium absorption, promoting bone growth	Rickets, bone pain, muscle weakness, increased risk of death from cardiovascular disease, cognitive impairment, asthma in children, cancer
E tocopherols	Seeds, nuts, vegetable oils, avocados, wheat germ	15 mg	Antioxidant	Anemia
K phylloquinone	Dark green leafy vegetables, broccoli, Brussels sprouts, cabbage	90–120 $\mu$ g	Blood clotting, bone health	Hemorrhagic disease of newborn in infants; uncommon in adults

Table 24.3

### Water-soluble Vitamins

Vitamin and alternative name	Sources	Recommended daily allowance	Function	Problems associated with deficiency
B <sub>1</sub> thiamine	Whole grains, enriched bread and cereals, milk, meat	1.1–1.2 mg	Carbohydrate metabolism	Beriberi, Wernicke-Korsikoff syndrome
B <sub>2</sub> riboflavin	Brewer's yeast, almonds, milk, organ meats, legumes, enriched breads and cereals, broccoli, asparagus	1.1–1.3 mg	Synthesis of FAD for metabolism, production of red blood cells	Fatigue, slowed growth, digestive problems, light sensitivity, epithelial problems like cracks in the corners of the mouth
B <sub>3</sub> niacin	Meat, fish, poultry, enriched breads and cereals, peanuts	14–16 mg	Synthesis of NAD, nerve function, cholesterol production	Cracked, scaly skin; dementia; diarrhea; also known as pellagra
B <sub>5</sub> pantothenic acid	Meat, poultry, potatoes, oats, enriched breads and cereals, tomatoes	5 mg	Synthesis of coenzyme A in fatty acid metabolism	Rare: symptoms may include fatigue, insomnia, depression, irritability
B <sub>6</sub> pyridoxine	Potatoes, bananas, beans, seeds, nuts, meat, poultry, fish, eggs, dark green leafy vegetables, soy, organ meats	1.3–1.5 mg	Sodium and potassium balance, red blood cell synthesis, protein metabolism	Confusion, irritability, depression, mouth and tongue sores

Table 24.4

## Water-soluble Vitamins

Vitamin and alternative name	Sources	Recommended daily allowance	Function	Problems associated with deficiency
B <sub>7</sub> biotin	Liver, fruits, meats	30 $\mu\text{g}$	Cell growth, metabolism of fatty acids, production of blood cells	Rare in developed countries; symptoms include dermatitis, hair loss, loss of muscular coordination
B <sub>9</sub> folic acid	Liver, legumes, dark green leafy vegetables, enriched breads and cereals, citrus fruits	400 $\mu\text{g}$	DNA/protein synthesis	Poor growth, gingivitis, appetite loss, shortness of breath, gastrointestinal problems, mental deficits
B <sub>12</sub> cyanocobalamin	Fish, meat, poultry, dairy products, eggs	2.4 $\mu\text{g}$	Fatty acid oxidation, nerve cell function, red blood cell production	Pernicious anemia, leading to nerve cell damage
C ascorbic acid	Citrus fruits, red berries, peppers, tomatoes, broccoli, dark green leafy vegetables	75–90 mg	Necessary to produce collagen for formation of connective tissue and teeth, and for wound healing	Dry hair, gingivitis, bleeding gums, dry and scaly skin, slow wound healing, easy bruising, compromised immunity; can lead to scurvy

**Table 24.4**

## Minerals

**Minerals** in food are inorganic compounds that work with other nutrients to ensure the body functions properly. Minerals cannot be made in the body; they come from the diet. The amount of minerals in the body is small—only 4 percent of the total body mass—and most of that consists of the minerals that the body requires in moderate quantities: potassium, sodium, calcium, phosphorus, magnesium, and chloride.

The most common minerals in the body are calcium and phosphorus, both of which are stored in the skeleton and necessary for the hardening of bones. Most minerals are ionized, and their ionic forms are used in physiological processes throughout the body. Sodium and chloride ions are electrolytes in the blood and extracellular tissues, and iron ions are critical to the formation of hemoglobin. There are additional trace minerals that are still important to the body's functions, but their required quantities are much lower.

Like vitamins, minerals can be consumed in toxic quantities (although it is rare). A healthy diet includes most of the minerals your body requires, so supplements and processed foods can add potentially toxic levels of minerals. **Table 24.5** and **Table 24.6** provide a summary of minerals and their function in the body.

## Major Minerals

Mineral	Sources	Recommended daily allowance	Function	Problems associated with deficiency
Potassium	Meats, some fish, fruits, vegetables, legumes, dairy products	4700 mg	Nerve and muscle function; acts as an electrolyte	Hypokalemia: weakness, fatigue, muscle cramping, gastrointestinal problems, cardiac problems
Sodium	Table salt, milk, beets, celery, processed foods	2300 mg	Blood pressure, blood volume, muscle and nerve function	Rare
Calcium	Dairy products, dark green leafy vegetables, blackstrap molasses, nuts, brewer's yeast, some fish	1000 mg	Bone structure and health; nerve and muscle functions, especially cardiac function	Slow growth, weak and brittle bones
Phosphorous	Meat, milk	700 mg	Bone formation, metabolism, ATP production	Rare
Magnesium	Whole grains, nuts, leafy green vegetables	310–420 mg	Enzyme activation, production of energy, regulation of other nutrients	Agitation, anxiety, sleep problems, nausea and vomiting, abnormal heart rhythms, low blood pressure, muscular problems
Chloride	Most foods, salt, vegetables, especially seaweed, tomatoes, lettuce, celery, olives	2300 mg	Balance of body fluids, digestion	Loss of appetite, muscle cramps

**Table 24.5**

## Trace Minerals

Mineral	Sources	Recommended daily allowance	Function	Problems associated with deficiency
Iron	Meat, poultry, fish, shellfish, legumes, nuts, seeds, whole grains, dark leafy green vegetables	8–18 mg	Transport of oxygen in blood, production of ATP	Anemia, weakness, fatigue
Zinc	Meat, fish, poultry, cheese, shellfish	8–11 mg	Immunity, reproduction, growth, blood clotting, insulin and thyroid function	Loss of appetite, poor growth, weight loss, skin problems, hair loss, vision problems, lack of taste or smell

**Table 24.6**

## Trace Minerals

Mineral	Sources	Recommended daily allowance	Function	Problems associated with deficiency
Copper	Seafood, organ meats, nuts, legumes, chocolate, enriched breads and cereals, some fruits and vegetables	900 $\mu\text{g}$	Red blood cell production, nerve and immune system function, collagen formation, acts as an antioxidant	Anemia, low body temperature, bone fractures, low white blood cell concentration, irregular heartbeat, thyroid problems
Iodine	Fish, shellfish, garlic, lima beans, sesame seeds, soybeans, dark leafy green vegetables	150 $\mu\text{g}$	Thyroid function	Hypothyroidism: fatigue, weight gain, dry skin, temperature sensitivity
Sulfur	Eggs, meat, poultry, fish, legumes	None	Component of amino acids	Protein deficiency
Fluoride	Fluoridated water	3–4 mg	Maintenance of bone and tooth structure	Increased cavities, weak bones and teeth
Manganese	Nuts, seeds, whole grains, legumes	1.8–2.3 mg	Formation of connective tissue and bones, blood clotting, sex hormone development, metabolism, brain and nerve function	Infertility, bone malformation, weakness, seizures
Cobalt	Fish, nuts, leafy green vegetables, whole grains	None	Component of B <sub>12</sub>	None
Selenium	Brewer's yeast, wheat germ, liver, butter, fish, shellfish, whole grains	55 $\mu\text{g}$	Antioxidant, thyroid function, immune system function	Muscle pain
Chromium	Whole grains, lean meats, cheese, black pepper, thyme, brewer's yeast	25–35 $\mu\text{g}$	Insulin function	High blood sugar, triglyceride, and cholesterol levels
Molybdenum	Legumes, whole grains, nuts	45 $\mu\text{g}$	Cofactor for enzymes	Rare

Table 24.6

## KEY TERMS

- absorptive state** also called the fed state; the metabolic state occurring during the first few hours after ingesting food in which the body is digesting food and absorbing the nutrients
- acetyl coenzyme A (acetyl CoA)** starting molecule of the Krebs cycle
- anabolic hormones** hormones that stimulate the synthesis of new, larger molecules
- anabolic reactions** reactions that build smaller molecules into larger molecules
- ATP synthase** protein pore complex that creates ATP
- basal metabolic rate (BMR)** amount of energy expended by the body at rest
- beta ( $\beta$ )-hydroxybutyrate** primary ketone body produced in the body
- beta ( $\beta$ )-oxidation** fatty acid oxidation
- bile salts** salts that are released from the liver in response to lipid ingestion and surround the insoluble triglycerides to aid in their conversion to monoglycerides and free fatty acids
- biosynthesis reactions** reactions that create new molecules, also called anabolic reactions
- body mass index (BMI)** relative amount of body weight compared to the overall height; a BMI ranging from 18–24.9 is considered normal weight, 25–29.9 is considered overweight, and greater than 30 is considered obese
- calorie** amount of heat it takes to raise 1 kg (1000 g) of water by 1 °C
- catabolic hormones** hormones that stimulate the breakdown of larger molecules
- catabolic reactions** reactions that break down larger molecules into their constituent parts
- cellular respiration** production of ATP from glucose oxidation via glycolysis, the Krebs cycle, and oxidative phosphorylation
- cholecystokinin (CCK)** hormone that stimulates the release of pancreatic lipase and the contraction of the gallbladder to release bile salts
- chylomicrons** vesicles containing cholesterol and triglycerides that transport lipids out of the intestinal cells and into the lymphatic and circulatory systems
- chymotrypsin** pancreatic enzyme that digests protein
- chymotrypsinogen** proenzyme that is activated by trypsin into chymotrypsin
- citric acid cycle** also called the Krebs cycle or the tricarboxylic acid cycle; converts pyruvate into CO<sub>2</sub> and high-energy FADH<sub>2</sub>, NADH, and ATP molecules
- conduction** transfer of heat through physical contact
- convection** transfer of heat between the skin and air or water
- elastase** pancreatic enzyme that digests protein
- electron transport chain (ETC)** ATP production pathway in which electrons are passed through a series of oxidation-reduction reactions that forms water and produces a proton gradient
- energy-consuming phase** first phase of glycolysis, in which two molecules of ATP are necessary to start the reaction
- energy-yielding phase** second phase of glycolysis, during which energy is produced
- enterokinase** enzyme located in the wall of the small intestine that activates trypsin

**evaporation** transfer of heat that occurs when water changes from a liquid to a gas

**FADH<sub>2</sub>** high-energy molecule needed for glycolysis

**fatty acid oxidation** breakdown of fatty acids into smaller chain fatty acids and acetyl CoA

**flavin adenine dinucleotide (FAD)** coenzyme used to produce FADH<sub>2</sub>

**glucokinase** cellular enzyme, found in the liver, which converts glucose into glucose-6-phosphate upon uptake into the cell

**gluconeogenesis** process of glucose synthesis from pyruvate or other molecules

**glucose-6-phosphate** phosphorylated glucose produced in the first step of glycolysis

**glycogen** form that glucose assumes when it is stored

**glycolysis** series of metabolic reactions that breaks down glucose into pyruvate and produces ATP

**hexokinase** cellular enzyme, found in most tissues, that converts glucose into glucose-6-phosphate upon uptake into the cell

**hydroxymethylglutaryl CoA (HMG CoA)** molecule created in the first step of the creation of ketone bodies from acetyl CoA

**inactive proenzymes** forms in which proteases are stored and released to prevent the inappropriate digestion of the native proteins of the stomach, pancreas, and small intestine

**insulin** hormone secreted by the pancreas that stimulates the uptake of glucose into the cells

**ketone bodies** alternative source of energy when glucose is limited, created when too much acetyl CoA is created during fatty acid oxidation

**Krebs cycle** also called the citric acid cycle or the tricarboxylic acid cycle, converts pyruvate into CO<sub>2</sub> and high-energy FADH<sub>2</sub>, NADH, and ATP molecules

**lipogenesis** synthesis of lipids that occurs in the liver or adipose tissues

**lipolysis** breakdown of triglycerides into glycerol and fatty acids

**metabolic rate** amount of energy consumed minus the amount of energy expended by the body

**metabolism** sum of all catabolic and anabolic reactions that take place in the body

**minerals** inorganic compounds required by the body to ensure proper function of the body

**monoglyceride molecules** lipid consisting of a single fatty acid chain attached to a glycerol backbone

**monosaccharide** smallest, monomeric sugar molecule

**NADH** high-energy molecule needed for glycolysis

**nicotinamide adenine dinucleotide (NAD)** coenzyme used to produce NADH

**oxidation** loss of an electron

**oxidation-reduction reaction** (also, redox reaction) pair of reactions in which an electron is passed from one molecule to another, oxidizing one and reducing the other

**oxidative phosphorylation** process that converts high-energy NADH and FADH<sub>2</sub> into ATP

**pancreatic lipases** enzymes released from the pancreas that digest lipids in the diet

**pepsin** enzyme that begins to break down proteins in the stomach

**polysaccharides** complex carbohydrates made up of many monosaccharides

**postabsorptive state** also called the fasting state; the metabolic state occurring after digestion when food is no longer the body's source of energy and it must rely on stored glycogen

**proteolysis** process of breaking proteins into smaller peptides

**pyruvate** three-carbon end product of glycolysis and starting material that is converted into acetyl CoA that enters the Krebs cycle

**radiation** transfer of heat via infrared waves

**reduction** gaining of an electron

**salivary amylase** digestive enzyme that is found in the saliva and begins the digestion of carbohydrates in the mouth

**secretin** hormone released in the small intestine to aid in digestion

**sodium bicarbonate** anion released into the small intestine to neutralize the pH of the food from the stomach

**terminal electron acceptor** oxygen, the recipient of the free hydrogen at the end of the electron transport chain

**thermoneutral** external temperature at which the body does not expend any energy for thermoregulation, about 84 °F

**thermoregulation** process of regulating the temperature of the body

**transamination** transfer of an amine group from one molecule to another as a way to turn nitrogen waste into ammonia so that it can enter the urea cycle

**tricarboxylic acid cycle (TCA)** also called the Krebs cycle or the citric acid cycle; converts pyruvate into CO<sub>2</sub> and high-energy FADH<sub>2</sub>, NADH, and ATP molecules

**triglycerides** lipids, or fats, consisting of three fatty acid chains attached to a glycerol backbone

**trypsin** pancreatic enzyme that activates chymotrypsin and digests protein

**trypsinogen** proenzyme form of trypsin

**urea cycle** process that converts potentially toxic nitrogen waste into urea that can be eliminated through the kidneys

**vitamins** organic compounds required by the body to perform biochemical reactions like metabolism and bone, cell, and tissue growth

## CHAPTER REVIEW

### 24.1 Overview of Metabolic Reactions

Metabolism is the sum of all catabolic (break down) and anabolic (synthesis) reactions in the body. The metabolic rate measures the amount of energy used to maintain life. An organism must ingest a sufficient amount of food to maintain its metabolic rate if the organism is to stay alive for very long.

Catabolic reactions break down larger molecules, such as carbohydrates, lipids, and proteins from ingested food, into their constituent smaller parts. They also include the breakdown of ATP, which releases the energy needed for metabolic processes in all cells throughout the body.

Anabolic reactions, or biosynthetic reactions, synthesize larger molecules from smaller constituent parts, using ATP as the energy source for these reactions. Anabolic reactions build bone, muscle mass, and new proteins, fats, and nucleic acids. Oxidation-reduction reactions transfer electrons across molecules by oxidizing one molecule and reducing another, and collecting the released energy to convert P<sub>i</sub> and ADP into ATP. Errors in metabolism alter the processing of carbohydrates, lipids, proteins, and nucleic acids, and can result in a number of disease states.

## 24.2 Carbohydrate Metabolism

Metabolic enzymes catalyze catabolic reactions that break down carbohydrates contained in food. The energy released is used to power the cells and systems that make up your body. Excess or unutilized energy is stored as fat or glycogen for later use. Carbohydrate metabolism begins in the mouth, where the enzyme salivary amylase begins to break down complex sugars into monosaccharides. These can then be transported across the intestinal membrane into the bloodstream and then to body tissues. In the cells, glucose, a six-carbon sugar, is processed through a sequence of reactions into smaller sugars, and the energy stored inside the molecule is released. The first step of carbohydrate catabolism is glycolysis, which produces pyruvate, NADH, and ATP. Under anaerobic conditions, the pyruvate can be converted into lactate to keep glycolysis working. Under aerobic conditions, pyruvate enters the Krebs cycle, also called the citric acid cycle or tricarboxylic acid cycle. In addition to ATP, the Krebs cycle produces high-energy FADH<sub>2</sub> and NADH molecules, which provide electrons to the oxidative phosphorylation process that generates more high-energy ATP molecules. For each molecule of glucose that is processed in glycolysis, a net of 36 ATPs can be created by aerobic respiration.

Under anaerobic conditions, ATP production is limited to those generated by glycolysis. While a total of four ATPs are produced by glycolysis, two are needed to begin glycolysis, so there is a net yield of two ATP molecules.

In conditions of low glucose, such as fasting, starvation, or low carbohydrate diets, glucose can be synthesized from lactate, pyruvate, glycerol, alanine, or glutamate. This process, called gluconeogenesis, is almost the reverse of glycolysis and serves to create glucose molecules for glucose-dependent organs, such as the brain, when glucose levels fall below normal.

## 24.3 Lipid Metabolism

Lipids are available to the body from three sources. They can be ingested in the diet, stored in the adipose tissue of the body, or synthesized in the liver. Fats ingested in the diet are digested in the small intestine. The triglycerides are broken down into monoglycerides and free fatty acids, then imported across the intestinal mucosa. Once across, the triglycerides are resynthesized and transported to the liver or adipose tissue. Fatty acids are oxidized through fatty acid or  $\beta$ -oxidation into two-carbon acetyl CoA molecules, which can then enter the Krebs cycle to generate ATP. If excess acetyl CoA is created and overloads the capacity of the Krebs cycle, the acetyl CoA can be used to synthesize ketone bodies. When glucose is limited, ketone bodies can be oxidized and used for fuel. Excess acetyl CoA generated from excess glucose or carbohydrate ingestion can be used for fatty acid synthesis or lipogenesis. Acetyl CoA is used to create lipids, triglycerides, steroid hormones, cholesterol, and bile salts. Lipolysis is the breakdown of triglycerides into glycerol and fatty acids, making them easier for the body to process.

## 24.4 Protein Metabolism

Digestion of proteins begins in the stomach, where HCl and pepsin begin the process of breaking down proteins into their constituent amino acids. As the chyme enters the small intestine, it mixes with bicarbonate and digestive enzymes. The bicarbonate neutralizes the acidic HCl, and the digestive enzymes break down the proteins into smaller peptides and amino acids. Digestive hormones secretin and CCK are released from the small intestine to aid in digestive processes, and digestive proenzymes are released from the pancreas (trypsinogen and chymotrypsinogen). Enterokinase, an enzyme located in the wall of the small intestine, activates trypsin, which in turn activates chymotrypsin. These enzymes liberate the individual amino acids that are then transported via sodium-amino acid transporters across the intestinal wall into the cell. The amino acids are then transported into the bloodstream for dispersal to the liver and cells throughout the body to be used to create new proteins. When in excess, the amino acids are processed and stored as glucose or ketones. The nitrogen waste that is liberated in this process is converted to urea in the urea acid cycle and eliminated in the urine. In times of starvation, amino acids can be used as an energy source and processed through the Krebs cycle.

## 24.5 Metabolic States of the Body

There are three main metabolic states of the body: absorptive (fed), postabsorptive (fasting), and starvation. During any given day, your metabolism switches between absorptive and postabsorptive states. Starvation states happen very rarely in generally well-nourished individuals. When the body is fed, glucose, fats, and proteins are absorbed across the intestinal membrane and enter the bloodstream and lymphatic system to be used immediately for fuel. Any excess is stored for later fasting stages. As blood glucose levels rise, the pancreas releases insulin to stimulate the uptake of glucose by hepatocytes in the liver, muscle cells/fibers, and adipocytes (fat cells), and to promote its conversion to glycogen. As the postabsorptive state begins, glucose levels drop, and there is a corresponding drop in insulin levels. Falling glucose levels trigger the pancreas to release glucagon to turn off glycogen synthesis in the liver and stimulate its breakdown into glucose. The glucose is released into the bloodstream to serve as a fuel source for cells throughout the body. If glycogen stores are depleted during fasting, alternative sources, including fatty acids and proteins, can be metabolized and used as fuel. When the body once again enters the absorptive state after fasting, fats and proteins are digested and used to replenish fat

and protein stores, whereas glucose is processed and used first to replenish the glycogen stores in the peripheral tissues, then in the liver. If the fast is not broken and starvation begins to set in, during the initial days, glucose produced from gluconeogenesis is still used by the brain and organs. After a few days, however, ketone bodies are created from fats and serve as the preferential fuel source for the heart and other organs, so that the brain can still use glucose. Once these stores are depleted, proteins will be catabolized first from the organs with fast turnover, such as the intestinal lining. Muscle will be spared to prevent the wasting of muscle tissue; however, these proteins will be used if alternative stores are not available.

## 24.6 Energy and Heat Balance

Some of the energy from the food that is ingested is used to maintain the core temperature of the body. Most of the energy derived from the food is released as heat. The core temperature is kept around 36.5–37.5 °C (97.7–99.5 °F). This is tightly regulated by the hypothalamus in the brain, which senses changes in the core temperature and operates like a thermostat to increase sweating or shivering, or inducing other mechanisms to return the temperature to its normal range. The body can also gain or lose heat through mechanisms of heat exchange. Conduction transfers heat from one object to another through physical contact. Convection transfers heat to air or water. Radiation transfers heat via infrared radiation. Evaporation transfers heat as water changes state from a liquid to a gas.

## 24.7 Nutrition and Diet

Nutrition and diet affect your metabolism. More energy is required to break down fats and proteins than carbohydrates; however, all excess calories that are ingested will be stored as fat in the body. On average, a person requires 1500 to 2000 calories for normal daily activity, although routine exercise will increase that amount. If you ingest more than that, the remainder is stored for later use. Conversely, if you ingest less than that, the energy stores in your body will be depleted. Both the quantity and quality of the food you eat affect your metabolism and can affect your overall health. Eating too much or too little can result in serious medical conditions, including cardiovascular disease, cancer, and diabetes.

Vitamins and minerals are essential parts of the diet. They are needed for the proper function of metabolic pathways in the body. Vitamins are not stored in the body, so they must be obtained from the diet or synthesized from precursors available in the diet. Minerals are also obtained from the diet, but they are also stored, primarily in skeletal tissues.

## REVIEW QUESTIONS

- A monosaccharide is formed from a polysaccharide in what kind of reaction?
  - oxidation–reduction reaction
  - anabolic reaction
  - catabolic reaction
  - biosynthetic reaction
- If anabolic reactions exceed catabolic reactions, the result will be \_\_\_\_\_.
  - weight loss
  - weight gain
  - metabolic rate change
  - development of disease
- When NAD becomes NADH, the coenzyme has been \_\_\_\_\_.
  - reduced
  - oxidized
  - metabolized
  - hydrolyzed
- Anabolic reactions use energy by \_\_\_\_\_.
  - turning ADP into ATP
  - removing a phosphate group from ATP
  - producing heat
  - breaking down molecules into smaller parts
- Glycolysis results in the production of two \_\_\_\_\_ molecules from a single molecule of glucose. In the absence of \_\_\_\_\_, the end product of glycolysis is \_\_\_\_\_.
  - acetyl CoA, pyruvate, lactate
  - ATP, carbon, pyruvate
  - pyruvate, oxygen, lactate
  - pyruvate, carbon, acetyl CoA
- The Krebs cycle converts \_\_\_\_\_ through a cycle of reactions. In the process, ATP, \_\_\_\_\_, and \_\_\_\_\_ are produced.
  - acetyl CoA; FAD, NAD
  - acetyl CoA; FADH<sub>2</sub>; NADH
  - pyruvate; NAD; FADH<sub>2</sub>
  - pyruvate; oxygen; oxaloacetate
- Which pathway produces the most ATP molecules?
  - lactic acid fermentation
  - the Krebs cycle
  - the electron transport chain
  - glycolysis

- 8.** Aerobic cellular respiration results in the production of these two products.
- NADH and FADH<sub>2</sub>
  - ATP and pyruvate
  - ATP and glucose
  - ATP and H<sub>2</sub>O
- 9.** When NAD<sup>+</sup> becomes NADH, the coenzyme has been \_\_\_\_\_.
- reduced
  - oxidized
  - metabolized
  - hydrolyzed
- 10.** Lipids in the diet can be \_\_\_\_\_.
- broken down into energy for the body
  - stored as triglycerides for later use
  - converted into acetyl CoA
  - all of the above
- 11.** The gallbladder provides \_\_\_\_\_ that aid(s) in transport of lipids across the intestinal membrane.
- lipases
  - cholesterol
  - proteins
  - bile salts
- 12.** Triglycerides are transported by chylomicrons because \_\_\_\_\_.
- they cannot move easily in the blood stream because they are fat based, while the blood is water based
  - they are too small to move by themselves
  - the chylomicrons contain enzymes they need for anabolism
  - they cannot fit across the intestinal membrane
- 13.** Which molecule produces the most ATP?
- carbohydrates
  - FADH<sub>2</sub>
  - triglycerides
  - NADH
- 14.** Which molecules can enter the Krebs cycle?
- chylomicrons
  - acetyl CoA
  - monoglycerides
  - ketone bodies
- 15.** Acetyl CoA can be converted to all of the following except \_\_\_\_\_.
- ketone bodies
  - fatty acids
  - polysaccharides
  - triglycerides
- 16.** Digestion of proteins begins in the \_\_\_\_\_ where \_\_\_\_\_ and \_\_\_\_\_ mix with food to break down protein into \_\_\_\_\_.
- stomach; amylase; HCl; amino acids
  - mouth; pepsin; HCl; fatty acids
  - stomach; lipase; HCl; amino acids
  - stomach; pepsin; HCl; amino acids
- 17.** Amino acids are needed to \_\_\_\_\_.
- build new proteins
  - serve as fat stores
  - supply energy for the cell
  - create red blood cells
- 18.** If an amino acid is not used to create new proteins, it can be \_\_\_\_\_.
- converted to acetyl CoA
  - converted to glucose or ketones
  - converted to nitrogen
  - stored to be used later
- 19.** During the absorptive state, glucose levels are \_\_\_\_\_, insulin levels are \_\_\_\_\_, and glucagon levels \_\_\_\_\_.
- high; low; stay the same
  - low; low; stay the same
  - high; high; are high
  - high; high; are low
- 20.** Starvation sets in after 3 to 4 days without food. Which hormones change in response to low glucose levels?
- glucagon and insulin
  - ketones and glucagon
  - insulin, glucose, and glucagon
  - insulin and ketones
- 21.** The postabsorptive state relies on stores of \_\_\_\_\_ in the \_\_\_\_\_.
- insulin; pancreas
  - glucagon; pancreas
  - glycogen; liver
  - glucose; liver
- 22.** The body's temperature is controlled by the \_\_\_\_\_. This temperature is always kept between \_\_\_\_\_.
- pituitary; 36.5–37.5 °C
  - hypothalamus; 97.7–99.5 °F
  - hypothalamus; 36.5–37.5 °F
  - pituitary; 97.7–99.5 °F
- 23.** Fever increases the body temperature and can induce chills to help cool the temperature back down. What other mechanisms are in place to regulate the body temperature?
- shivering
  - sweating
  - erection of the hairs on the arms and legs
  - all of the above

- 24.** The heat you feel on your chair when you stand up was transferred from your skin via \_\_\_\_\_.
- conduction
  - convection
  - radiation
  - evaporation
- 25.** A crowded room warms up through the mechanism of \_\_\_\_\_.
- conduction
  - convection
  - radiation
  - evaporation
- 26.** A deficiency in vitamin A can result in \_\_\_\_\_.
- improper bone development
  - scurvy
  - improper eye development or sight
  - all of the above
- 27.** Rickets results in improper bone development in children that arises from the malabsorption of calcium and a deficiency in \_\_\_\_\_.
- vitamin D
  - vitamin C
  - vitamin B<sub>12</sub>
  - niacin
- 28.** Consuming which type of food will help the most with weight loss?
- fats
  - vegetables
  - lean meats
  - fruits
- 29.** Which of the following is stored in the body?
- thiamine
  - phosphorous
  - folic acid
  - vitamin C

## CRITICAL THINKING QUESTIONS

- 30.** Describe how metabolism can be altered.
- 31.** Describe how Addison's disease can be treated.
- 32.** Explain how glucose is metabolized to yield ATP.
- 33.** Insulin is released when food is ingested and stimulates the uptake of glucose into the cell. Discuss the mechanism cells employ to create a concentration gradient to ensure continual uptake of glucose from the bloodstream.
- 34.** Discuss how carbohydrates can be stored as fat.
- 35.** If a diabetic's breath smells like alcohol, what could this mean?
- 36.** Amino acids are not stored in the body. Describe how excess amino acids are processed in the cell.
- 37.** Release of trypsin and chymotrypsin in their active form can result in the digestion of the pancreas or small intestine itself. What mechanism does the body employ to prevent its self-destruction?
- 38.** In type II diabetes, insulin is produced but is nonfunctional. These patients are described as "starving in a sea of plenty," because their blood glucose levels are high, but none of the glucose is transported into the cells. Describe how this leads to malnutrition.
- 39.** Ketone bodies are used as an alternative source of fuel during starvation. Describe how ketones are synthesized.
- 40.** How does vasoconstriction help increase the core temperature of the body?
- 41.** How can the ingestion of food increase the body temperature?
- 42.** Weight loss and weight gain are complex processes. What are some of the main factors that influence weight gain in people?
- 43.** Some low-fat or non-fat foods contain a large amount of sugar to replace the fat content of the food. Discuss how this leads to increased fat in the body (and weight gain) even though the item is non-fat.

# 25 | THE URINARY SYSTEM



**Figure 25.1 Sewage Treatment Plant** (credit: "eutrophication&hypoxia"/flickr.com)

## Introduction

### Chapter Objectives

After studying this chapter, you will be able to:

- Describe the composition of urine
- Label structures of the urinary system
- Characterize the roles of each of the parts of the urinary system
- Illustrate the macroscopic and microscopic structures of the kidney
- Trace the flow of blood through the kidney
- Outline how blood is filtered in the kidney nephron
- Provide symptoms of kidney failure
- List some of the solutes filtered, secreted, and reabsorbed in different parts of the nephron
- Describe the role of a portal system in the kidney
- Explain how urine osmolarity is hormonally regulated
- Describe the regulation of major ions by the kidney
- Summarize the role of the kidneys in maintaining acid–base balance

The urinary system has roles you may be well aware of: cleansing the blood and ridding the body of wastes probably come to mind. However, there are additional, equally important functions played by the system. Take for example, regulation of pH, a function shared with the lungs and the buffers in the blood. Additionally, the regulation of blood pressure is a role shared with the heart and blood vessels. What about regulating the concentration of solutes in the blood? Did you know that the kidney is important in determining the concentration of red blood cells? Eighty-five percent of the erythropoietin (EPO) produced to stimulate red blood cell production is produced in the kidneys. The kidneys also perform the final synthesis step of vitamin D production, converting calcidiol to calcitriol, the active form of vitamin D.

If the kidneys fail, these functions are compromised or lost altogether, with devastating effects on homeostasis. The affected individual might experience weakness, lethargy, shortness of breath, anemia, widespread edema (swelling), metabolic acidosis, rising potassium levels, heart arrhythmias, and more. Each of these functions is vital to your well-being and survival. The urinary system, controlled by the nervous system, also stores urine until a convenient time for disposal and then provides the anatomical structures to transport this waste liquid to the outside of the body. Failure of nervous control or the anatomical structures leading to a loss of control of urination results in a condition called incontinence.

This chapter will help you to understand the anatomy of the urinary system and how it enables the physiologic functions critical to homeostasis. It is best to think of the kidney as a regulator of plasma makeup rather than simply a urine producer. As you read each section, ask yourself this question: “What happens if this does not work?” This question will help you to understand how the urinary system maintains homeostasis and affects all the other systems of the body and the quality of one’s life.



Watch this **video** (<http://openstaxcollege.org/l/urineintro>) from the Howard Hughes Medical Institute for an introduction to the urinary system.

## 25.1 | Physical Characteristics of Urine

By the end of this section, you will be able to:

- Compare and contrast blood plasma, glomerular filtrate, and urine characteristics
- Describe the characteristics of a normal urine sample, including normal range of pH, osmolarity, and volume

The urinary system’s ability to filter the blood resides in about 2 to 3 million tufts of specialized capillaries—the glomeruli—distributed more or less equally between the two kidneys. Because the glomeruli filter the blood based mostly on particle size, large elements like blood cells, platelets, antibodies, and albumen are excluded. The glomerulus is the first part of the nephron, which then continues as a highly specialized tubular structure responsible for creating the final urine composition. All other solutes, such as ions, amino acids, vitamins, and wastes, are filtered to create a filtrate composition very similar to plasma. The glomeruli create about 200 liters (189 quarts) of this filtrate every day, yet you excrete less than two liters of waste you call urine.

Characteristics of the urine change, depending on influences such as water intake, exercise, environmental temperature, nutrient intake, and other factors (**Table 25.1**). Some of the characteristics such as color and odor are rough descriptors of your state of hydration. For example, if you exercise or work outside, and sweat a great deal, your urine will turn darker and produce a slight odor, even if you drink plenty of water. Athletes are often advised to consume water until their urine is clear. This is good advice; however, it takes time for the kidneys to process body fluids and store it in the bladder. Another way of looking at this is that the quality of the urine produced is an average over the time it takes to make that urine. Producing

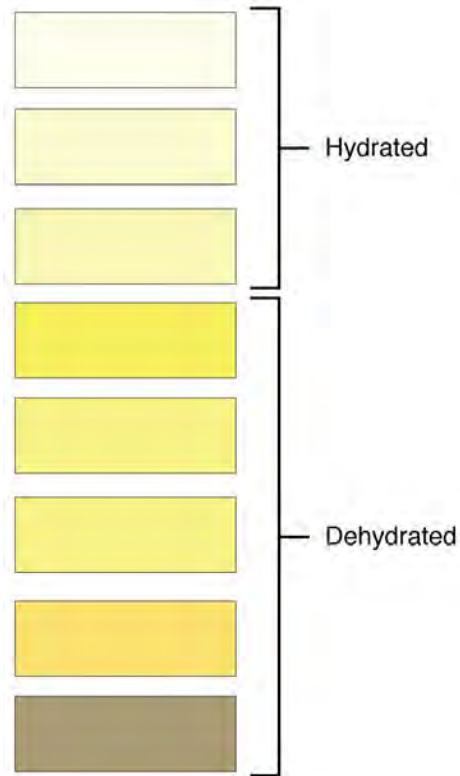
clear urine may take only a few minutes if you are drinking a lot of water or several hours if you are working outside and not drinking much.

### Normal Urine Characteristics

Characteristic	Normal values
Color	Pale yellow to deep amber
Odor	Odorless
Volume	750–2000 mL/24 hour
pH	4.5–8.0
Specific gravity	1.003–1.032
Osmolarity	40–1350 mOsmol/kg
Urobilinogen	0.2–1.0 mg/100 mL
White blood cells	0–2 HPF (per high-power field of microscope)
Leukocyte esterase	None
Protein	None or trace
Bilirubin	<0.3 mg/100 mL
Ketones	None
Nitrites	None
Blood	None
Glucose	None

**Table 25.1**

**Urinalysis** (urine analysis) often provides clues to renal disease. Normally, only traces of protein are found in urine, and when higher amounts are found, damage to the glomeruli is the likely basis. Unusually large quantities of urine may point to diseases like diabetes mellitus or hypothalamic tumors that cause diabetes insipidus. The color of urine is determined mostly by the breakdown products of red blood cell destruction (**Figure 25.2**). The “heme” of hemoglobin is converted by the liver into water-soluble forms that can be excreted into the bile and indirectly into the urine. This yellow pigment is **urochrome**. Urine color may also be affected by certain foods like beets, berries, and fava beans. A kidney stone or a cancer of the urinary system may produce sufficient bleeding to manifest as pink or even bright red urine. Diseases of the liver or obstructions of bile drainage from the liver impart a dark “tea” or “cola” hue to the urine. Dehydration produces darker, concentrated urine that may also possess the slight odor of ammonia. Most of the ammonia produced from protein breakdown is converted into urea by the liver, so ammonia is rarely detected in fresh urine. The strong ammonia odor you may detect in bathrooms or alleys is due to the breakdown of urea into ammonia by bacteria in the environment. About one in five people detect a distinctive odor in their urine after consuming asparagus; other foods such as onions, garlic, and fish can impart their own aromas! These food-caused odors are harmless.



**Figure 25.2 Urine Color**

Urine volume varies considerably. The normal range is one to two liters per day (**Table 25.2**). The kidneys must produce a minimum urine volume of about 500 mL/day to rid the body of wastes. Output below this level may be caused by severe dehydration or renal disease and is termed **oliguria**. The virtual absence of urine production is termed **anuria**. Excessive urine production is **polyuria**, which may be due to diabetes mellitus or diabetes insipidus. In diabetes mellitus, blood glucose levels exceed the number of available sodium-glucose transporters in the kidney, and glucose appears in the urine. The osmotic nature of glucose attracts water, leading to its loss in the urine. In the case of diabetes insipidus, insufficient pituitary antidiuretic hormone (ADH) release or insufficient numbers of ADH receptors in the collecting ducts means that too few water channels are inserted into the cell membranes that line the collecting ducts of the kidney. Insufficient numbers of water channels (aquaporins) reduce water absorption, resulting in high volumes of very dilute urine.

### Urine Volumes

Volume condition	Volume	Causes
Normal	1–2 L/day	
Polyuria	>2.5 L/day	Diabetes mellitus; diabetes insipidus; excess caffeine or alcohol; kidney disease; certain drugs, such as diuretics; sickle cell anemia; excessive water intake
Oliguria	300–500 mL/day	Dehydration; blood loss; diarrhea; cardiogenic shock; kidney disease; enlarged prostate
Anuria	<50 mL/day	Kidney failure; obstruction, such as kidney stone or tumor; enlarged prostate

**Table 25.2**

The pH (hydrogen ion concentration) of the urine can vary more than 1000-fold, from a normal low of 4.5 to a maximum of 8.0. Diet can influence pH; meats lower the pH, whereas citrus fruits, vegetables, and dairy products raise the pH.

Chronically high or low pH can lead to disorders, such as the development of kidney stones or osteomalacia.

Specific gravity is a measure of the quantity of solutes per unit volume of a solution and is traditionally easier to measure than osmolarity. Urine will always have a specific gravity greater than pure water (water = 1.0) due to the presence of solutes. Laboratories can now measure urine osmolarity directly, which is a more accurate indicator of urinary solutes than **specific gravity**. Remember that osmolarity is the number of osmoles or milliosmoles per liter of fluid (mOsmol/L). Urine osmolarity ranges from a low of 50–100 mOsmol/L to as high as 1200 mOsmol/L H<sub>2</sub>O.

Cells are not normally found in the urine. The presence of leukocytes may indicate a urinary tract infection. **Leukocyte esterase** is released by leukocytes; if detected in the urine, it can be taken as indirect evidence of a urinary tract infection (UTI).

Protein does not normally leave the glomerular capillaries, so only trace amounts of protein should be found in the urine, approximately 10 mg/100 mL in a random sample. If excessive protein is detected in the urine, it usually means that the glomerulus is damaged and is allowing protein to “leak” into the filtrate.

Ketones are byproducts of fat metabolism. Finding ketones in the urine suggests that the body is using fat as an energy source in preference to glucose. In diabetes mellitus when there is not enough insulin (type I diabetes mellitus) or because of insulin resistance (type II diabetes mellitus), there is plenty of glucose, but without the action of insulin, the cells cannot take it up, so it remains in the bloodstream. Instead, the cells are forced to use fat as their energy source, and fat consumed at such a level produces excessive ketones as byproducts. These excess ketones will appear in the urine. Ketones may also appear if there is a severe deficiency of proteins or carbohydrates in the diet.

Nitrates (NO<sub>3</sub><sup>-</sup>) occur normally in the urine. Gram-negative bacteria metabolize nitrate into nitrite (NO<sub>2</sub><sup>-</sup>), and its presence in the urine is indirect evidence of infection.

There should be no blood found in the urine. It may sometimes appear in urine samples as a result of menstrual contamination, but this is not an abnormal condition. Now that you understand what the normal characteristics of urine are, the next section will introduce you to how you store and dispose of this waste product and how you make it.

## 25.2 | Gross Anatomy of Urine Transport

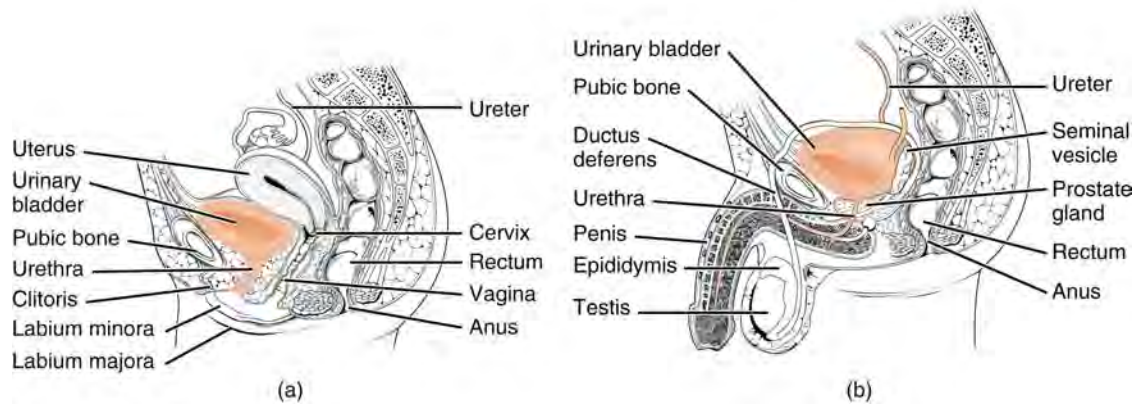
By the end of this section, you will be able to:

- Identify the ureters, urinary bladder, and urethra, as well as their location, structure, histology, and function
- Compare and contrast male and female urethras
- Describe the micturition reflex
- Describe voluntary and involuntary neural control of micturition

Rather than start with urine formation, this section will start with urine excretion. Urine is a fluid of variable composition that requires specialized structures to remove it from the body safely and efficiently. Blood is filtered, and the filtrate is transformed into urine at a relatively constant rate throughout the day. This processed liquid is stored until a convenient time for excretion. All structures involved in the transport and storage of the urine are large enough to be visible to the naked eye. This transport and storage system not only stores the waste, but it protects the tissues from damage due to the wide range of pH and osmolarity of the urine, prevents infection by foreign organisms, and for the male, provides reproductive functions.

### Urethra

The **urethra** transports urine from the bladder to the outside of the body for disposal. The urethra is the only urologic organ that shows any significant anatomic difference between males and females; all other urine transport structures are identical (**Figure 25.3**).



**Figure 25.3 Female and Male Urethras** The urethra transports urine from the bladder to the outside of the body. This image shows (a) a female urethra and (b) a male urethra.

The urethra in both males and females begins inferior and central to the two ureteral openings forming the three points of a triangular-shaped area at the base of the bladder called the **trigone** (Greek tri- = “triangle” and the root of the word “trigonometry”). The urethra tracks posterior and inferior to the pubic symphysis (see **Figure 25.3a**). In both males and females, the proximal urethra is lined by transitional epithelium, whereas the terminal portion is a nonkeratinized, stratified squamous epithelium. In the male, pseudostratified columnar epithelium lines the urethra between these two cell types. Voiding is regulated by an involuntary autonomic nervous system-controlled **internal urinary sphincter**, consisting of smooth muscle and voluntary skeletal muscle that forms the **external urinary sphincter** below it.

### Female Urethra

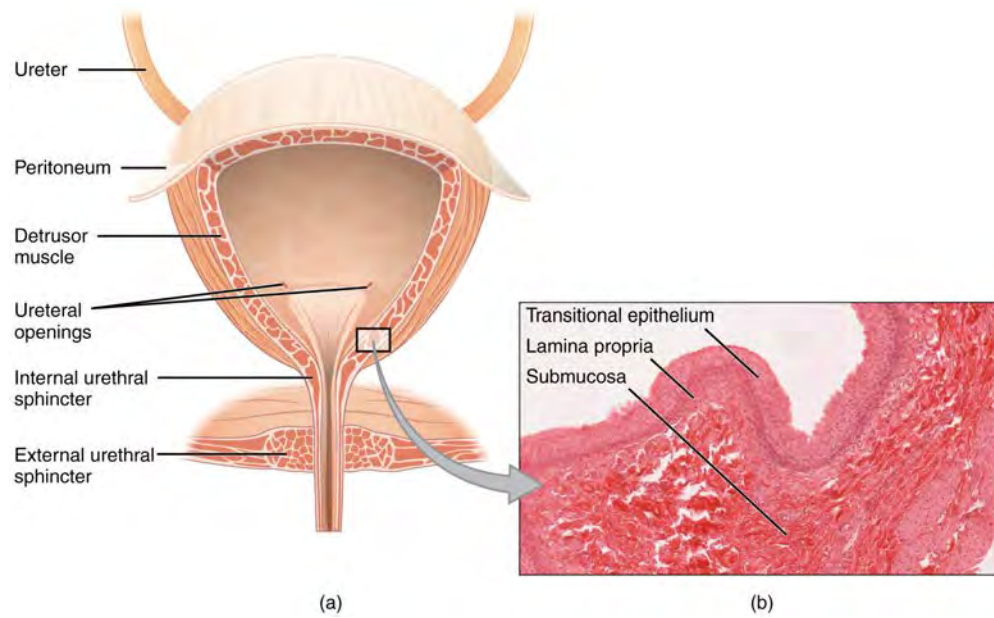
The external urethral orifice is embedded in the anterior vaginal wall inferior to the clitoris, superior to the vaginal opening (introitus), and medial to the labia minora. Its short length, about 4 cm, is less of a barrier to fecal bacteria than the longer male urethra and the best explanation for the greater incidence of UTI in women. Voluntary control of the external urethral sphincter is a function of the pudendal nerve. It arises in the sacral region of the spinal cord, traveling via the S2–S4 nerves of the sacral plexus.

### Male Urethra

The male urethra passes through the prostate gland immediately inferior to the bladder before passing below the pubic symphysis (see **Figure 25.3b**). The length of the male urethra varies between men but averages 20 cm in length. It is divided into four regions: the preprostatic urethra, the prostatic urethra, the membranous urethra, and the spongy or penile urethra. The preprostatic urethra is very short and incorporated into the bladder wall. The prostatic urethra passes through the prostate gland. During sexual intercourse, it receives sperm via the ejaculatory ducts and secretions from the seminal vesicles. Paired Cowper’s glands (bulbourethral glands) produce and secrete mucus into the urethra to buffer urethral pH during sexual stimulation. The mucus neutralizes the usually acidic environment and lubricates the urethra, decreasing the resistance to ejaculation. The membranous urethra passes through the deep muscles of the perineum, where it is invested by the overlying urethral sphincters. The spongy urethra exits at the tip (external urethral orifice) of the penis after passing through the corpus spongiosum. Mucous glands are found along much of the length of the urethra and protect the urethra from extremes of urine pH. Innervation is the same in both males and females.

### Bladder

The urinary bladder collects urine from both ureters (**Figure 25.4**). The bladder lies anterior to the uterus in females, posterior to the pubic bone and anterior to the rectum. During late pregnancy, its capacity is reduced due to compression by the enlarging uterus, resulting in increased frequency of urination. In males, the anatomy is similar, minus the uterus, and with the addition of the prostate inferior to the bladder. The bladder is partially **retroperitoneal** (outside the peritoneal cavity) with its peritoneal-covered “dome” projecting into the abdomen when the bladder is distended with urine.



**Figure 25.4 Bladder** (a) Anterior cross section of the bladder. (b) The detrusor muscle of the bladder (source: monkey tissue) LM  $\times$  448. (Micrograph provided by the Regents of the University of Michigan Medical School  $\copyright$  2012)

## Interactive LINK



View the University of Michigan WebScope at [http://141.214.65.171/Histology/Urinary%20System/212N\\_HISTO\\_40X.svs/view.apml](http://141.214.65.171/Histology/Urinary%20System/212N_HISTO_40X.svs/view.apml) (<http://openstaxcollege.org/l/bladderMG>) to explore the tissue sample in greater detail.

The bladder is a highly distensible organ comprised of irregular crisscrossing bands of smooth muscle collectively called the **detrusor muscle**. The interior surface is made of transitional cellular epithelium that is structurally suited for the large volume fluctuations of the bladder. When empty, it resembles columnar epithelia, but when stretched, it “transitions” (hence the name) to a squamous appearance (see **Figure 25.4**). Volumes in adults can range from nearly zero to 500–600 mL.

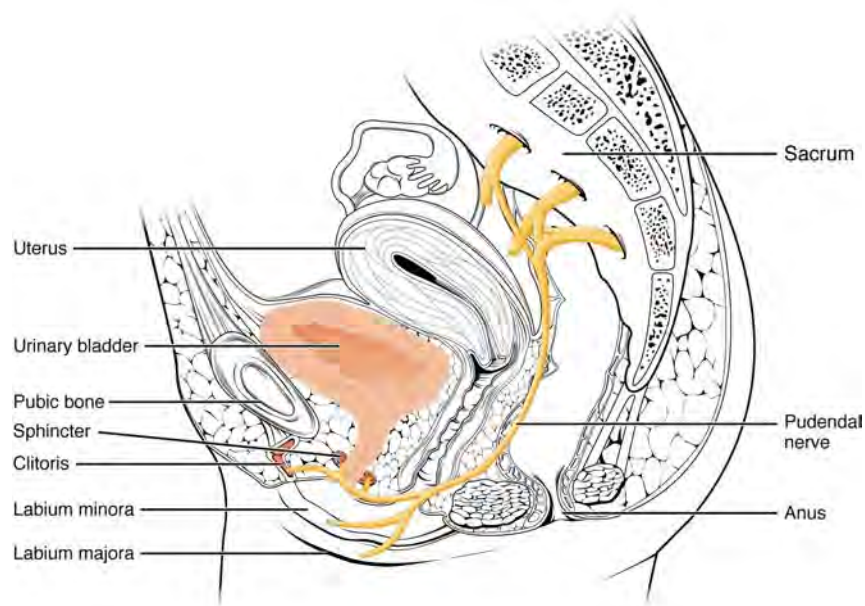
The detrusor muscle contracts with significant force in the young. The bladder’s strength diminishes with age, but voluntary contractions of abdominal skeletal muscles can increase intra-abdominal pressure to promote more forceful bladder emptying. Such voluntary contraction is also used in forceful defecation and childbirth.

### Micturition Reflex

**Micturition** is a less-often used, but proper term for urination or voiding. It results from an interplay of involuntary and voluntary actions by the internal and external urethral sphincters. When bladder volume reaches about 150 mL, an urge to void is sensed but is easily overridden. Voluntary control of urination relies on consciously preventing relaxation of the external urethral sphincter to maintain urinary continence. As the bladder fills, subsequent urges become harder to ignore. Ultimately, voluntary constraint fails with resulting **incontinence**, which will occur as bladder volume approaches 300 to 400 mL.

Normal micturition is a result of stretch receptors in the bladder wall that transmit nerve impulses to the sacral region of the spinal cord to generate a spinal reflex. The resulting parasympathetic neural outflow causes contraction of the detrusor muscle and relaxation of the involuntary internal urethral sphincter. At the same time, the spinal cord inhibits somatic motor neurons, resulting in the relaxation of the skeletal muscle of the external urethral sphincter. The micturition reflex is active in infants but with maturity, children learn to override the reflex by asserting external sphincter control, thereby delaying voiding (potty training). This reflex may be preserved even in the face of spinal cord injury that results in paraplegia or quadriplegia. However, relaxation of the external sphincter may not be possible in all cases, and therefore, periodic catheterization may be necessary for bladder emptying.

Nerves involved in the control of urination include the hypogastric, pelvic, and pudendal (**Figure 25.5**). Voluntary micturition requires an intact spinal cord and functional pudendal nerve arising from the **sacral micturition center**. Since the external urinary sphincter is voluntary skeletal muscle, actions by cholinergic neurons maintain contraction (and thereby continence) during filling of the bladder. At the same time, sympathetic nervous activity via the hypogastric nerves suppresses contraction of the detrusor muscle. With further bladder stretch, afferent signals traveling over sacral pelvic nerves activate parasympathetic neurons. This activates efferent neurons to release acetylcholine at the neuromuscular junctions, producing detrusor contraction and bladder emptying.

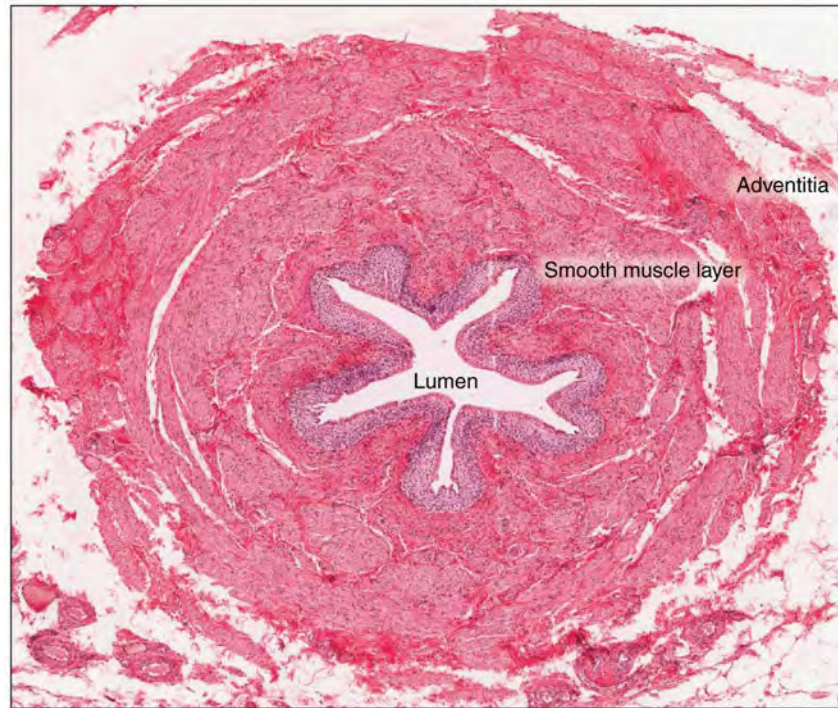


**Figure 25.5 Nerves Innervating the Urinary System**

## Ureters

The kidneys and ureters are completely retroperitoneal, and the bladder has a peritoneal covering only over the dome. As urine is formed, it drains into the calyces of the kidney, which merge to form the funnel-shaped renal pelvis in the hilum of each kidney. The renal pelvis narrows to become the ureter of each kidney. As urine passes through the ureter, it does not passively drain into the bladder but rather is propelled by waves of peristalsis. As the ureters enter the pelvis, they sweep laterally, hugging the pelvic walls. As they approach the bladder, they turn medially and pierce the bladder wall obliquely. This is important because it creates an one-way valve (a **physiological sphincter** rather than an **anatomical sphincter**) that allows urine into the bladder but prevents reflux of urine from the bladder back into the ureter. Children born lacking this oblique course of the ureter through the bladder wall are susceptible to “vesicoureteral reflux,” which dramatically increases their risk of serious UTI. Pregnancy also increases the likelihood of reflux and UTI.

The ureters are approximately 30 cm long. The inner mucosa is lined with transitional epithelium (**Figure 25.6**) and scattered goblet cells that secrete protective mucus. The muscular layer of the ureter consists of longitudinal and circular smooth muscles that create the peristaltic contractions to move the urine into the bladder without the aid of gravity. Finally, a loose adventitial layer composed of collagen and fat anchors the ureters between the parietal peritoneum and the posterior abdominal wall.



**Figure 25.6 Ureter** Peristaltic contractions help to move urine through the lumen with contributions from fluid pressure and gravity. LM  $\times$  128. (Micrograph provided by the Regents of the University of Michigan Medical School  $\copyright$  2012)

## 25.3 | Gross Anatomy of the Kidney

By the end of this section, you will be able to:

- Describe the external structure of the kidney, including its location, support structures, and covering
- Identify the major internal divisions and structures of the kidney
- Identify the major blood vessels associated with the kidney and trace the path of blood through the kidney
- Compare and contrast the cortical and juxtamedullary nephrons
- Name structures found in the cortex and medulla
- Describe the physiological characteristics of the cortex and medulla

The kidneys lie on either side of the spine in the retroperitoneal space between the parietal peritoneum and the posterior abdominal wall, well protected by muscle, fat, and ribs. They are roughly the size of your fist, and the male kidney is typically a bit larger than the female kidney. The kidneys are well vascularized, receiving about 25 percent of the cardiac output at rest.

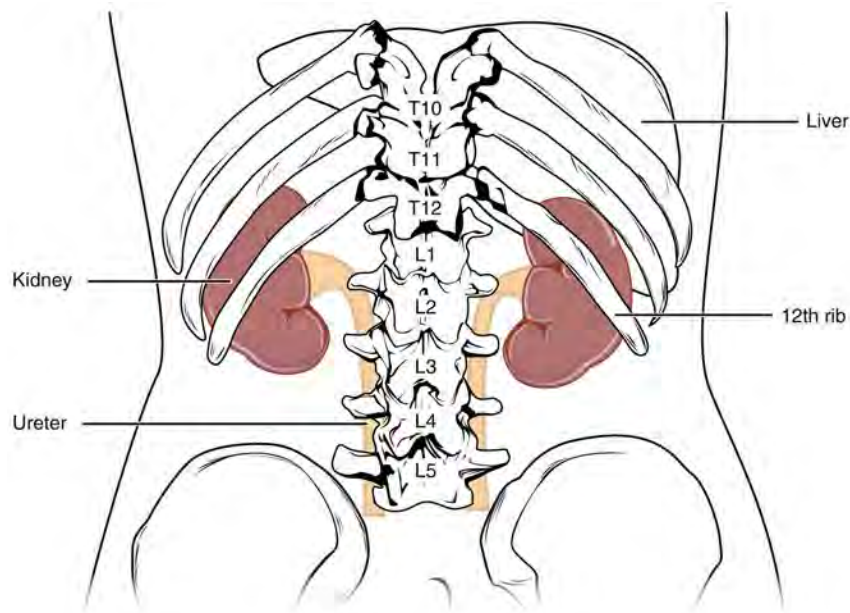
## Interactive LINK



There have never been sufficient kidney donations to provide a kidney to each person needing one. Watch this **video** (<http://openstaxcollege.org/l/TED>) to learn about the TED (Technology, Entertainment, Design) Conference held in March 2011. In this video, Dr. Anthony Atala discusses a cutting-edge technique in which a new kidney is “printed.” The successful utilization of this technology is still several years in the future, but imagine a time when you can print a replacement organ or tissue on demand.

### External Anatomy

The left kidney is located at about the T12 to L3 vertebrae, whereas the right is lower due to slight displacement by the liver. Upper portions of the kidneys are somewhat protected by the eleventh and twelfth ribs (**Figure 25.7**). Each kidney weighs about 125–175 g in males and 115–155 g in females. They are about 11–14 cm in length, 6 cm wide, and 4 cm thick, and are directly covered by a fibrous capsule composed of dense, irregular connective tissue that helps to hold their shape and protect them. This capsule is covered by a shock-absorbing layer of adipose tissue called the **renal fat pad**, which in turn is encompassed by a tough renal fascia. The fascia and, to a lesser extent, the overlying peritoneum serve to firmly anchor the kidneys to the posterior abdominal wall in a retroperitoneal position.



**Figure 25.7 Kidneys** The kidneys are slightly protected by the ribs and are surrounded by fat for protection (not shown).

On the superior aspect of each kidney is the adrenal gland. The adrenal cortex directly influences renal function through the production of the hormone aldosterone to stimulate sodium reabsorption.

## Internal Anatomy

A frontal section through the kidney reveals an outer region called the **renal cortex** and an inner region called the **medulla** (Figure 25.8). The **renal columns** are connective tissue extensions that radiate downward from the cortex through the medulla to separate the most characteristic features of the medulla, the **renal pyramids** and **renal papillae**. The papillae are bundles of collecting ducts that transport urine made by nephrons to the **calyces** of the kidney for excretion. The renal columns also serve to divide the kidney into 6–8 lobes and provide a supportive framework for vessels that enter and exit the cortex. The pyramids and renal columns taken together constitute the kidney lobes.

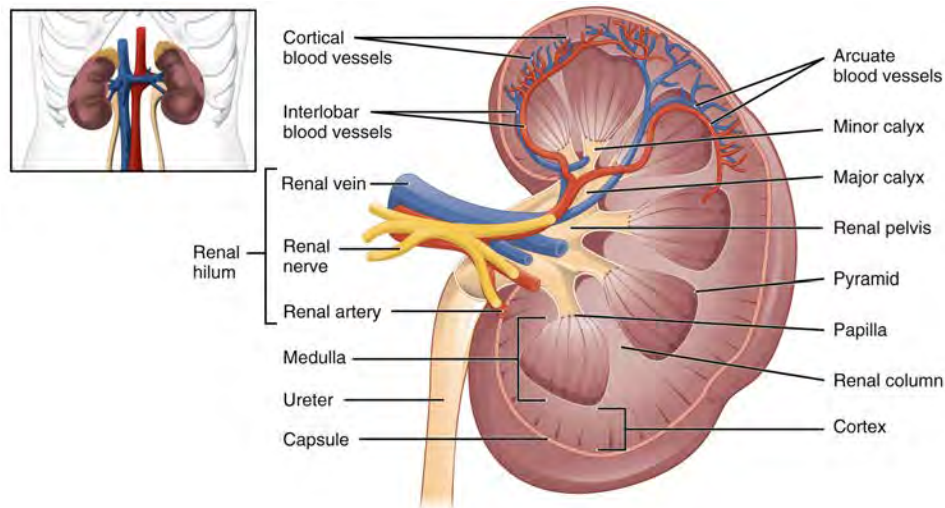


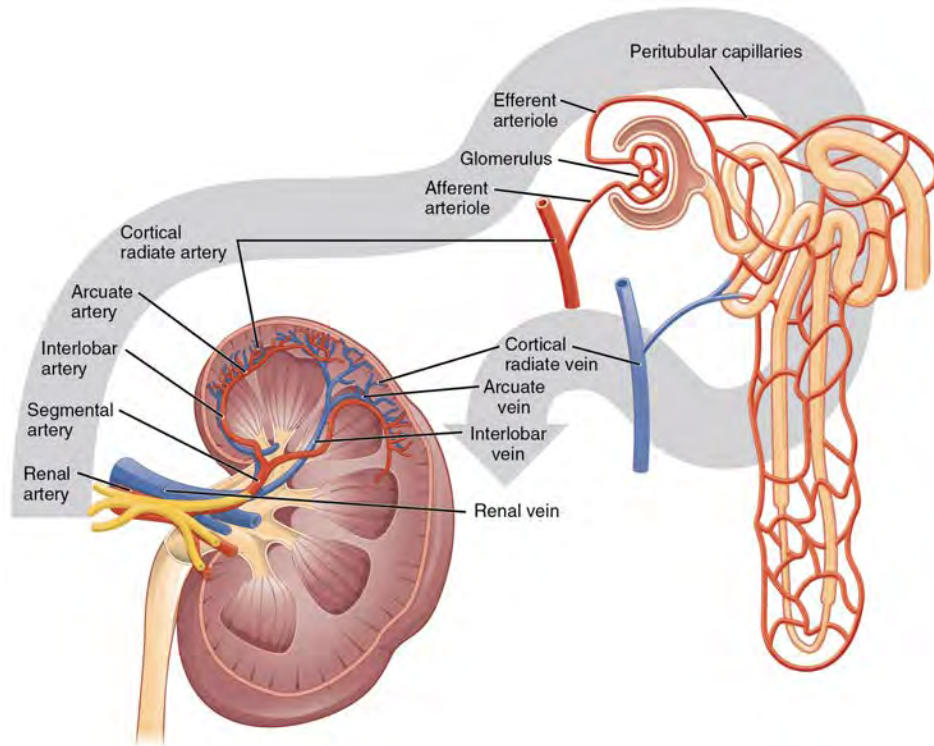
Figure 25.8 Left Kidney

## Renal Hilum

The **renal hilum** is the entry and exit site for structures servicing the kidneys: vessels, nerves, lymphatics, and ureters. The medial-facing hila are tucked into the sweeping convex outline of the cortex. Emerging from the hilum is the renal pelvis, which is formed from the major and minor calyces in the kidney. The smooth muscle in the renal pelvis funnels urine via peristalsis into the ureter. The renal arteries form directly from the descending aorta, whereas the renal veins return cleansed blood directly to the inferior vena cava. The artery, vein, and renal pelvis are arranged in an anterior-to-posterior order.

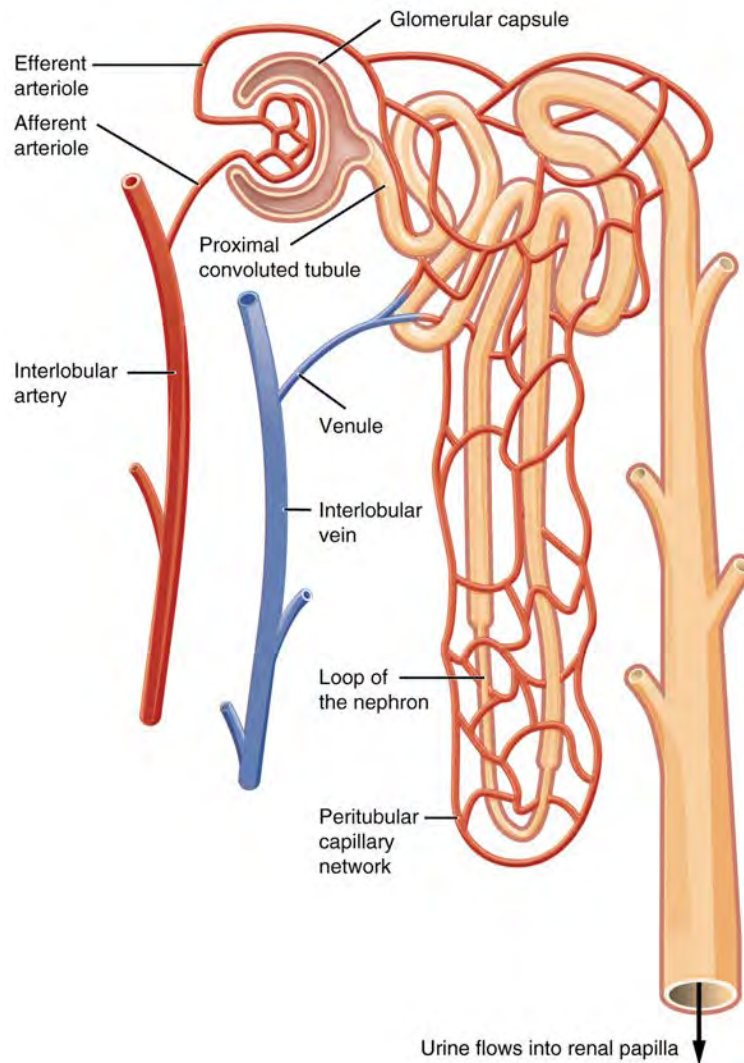
## Nephrons and Vessels

The renal artery first divides into segmental arteries, followed by further branching to form interlobar arteries that pass through the renal columns to reach the cortex (Figure 25.9). The interlobar arteries, in turn, branch into arcuate arteries, cortical radiate arteries, and then into afferent arterioles. The afferent arterioles service about 1.3 million nephrons in each kidney.



**Figure 25.9 Blood Flow in the Kidney**

**Nephrons** are the “functional units” of the kidney; they cleanse the blood and balance the constituents of the circulation. The afferent arterioles form a tuft of high-pressure capillaries about 200  $\mu\text{m}$  in diameter, the **glomerulus**. The rest of the nephron consists of a continuous sophisticated tubule whose proximal end surrounds the glomerulus in an intimate embrace—this is **Bowman’s capsule**. The glomerulus and Bowman’s capsule together form the **renal corpuscle**. As mentioned earlier, these glomerular capillaries filter the blood based on particle size. After passing through the renal corpuscle, the capillaries form a second arteriole, the **efferent arteriole** (Figure 25.10). These will next form a capillary network around the more distal portions of the nephron tubule, the **peritubular capillaries** and **vasa recta**, before returning to the venous system. As the glomerular filtrate progresses through the nephron, these capillary networks recover most of the solutes and water, and return them to the circulation. Since a capillary bed (the glomerulus) drains into a vessel that in turn forms a second capillary bed, the definition of a portal system is met. This is the only portal system in which an arteriole is found between the first and second capillary beds. (Portal systems also link the hypothalamus to the anterior pituitary, and the blood vessels of the digestive viscera to the liver.)



**Figure 25.10 Blood Flow in the Nephron** The two capillary beds are clearly shown in this figure. The efferent arteriole is the connecting vessel between the glomerulus and the peritubular capillaries and vasa recta.

## Interactive LINK



Visit this [link \(http://openstaxcollege.org/l/bloodflow5\)](http://openstaxcollege.org/l/bloodflow5) to view an interactive tutorial of the flow of blood through the kidney.

### Cortex

In a dissected kidney, it is easy to identify the cortex; it appears lighter in color compared to the rest of the kidney.

All of the renal corpuscles as well as both the **proximal convoluted tubules (PCTs)** and **distal convoluted tubules** are found here. Some nephrons have a short **loop of Henle** that does not dip beyond the cortex. These nephrons are called **cortical nephrons**. About 15 percent of nephrons have long loops of Henle that extend deep into the medulla and are called **juxtamedullary nephrons**.

## 25.4 | Microscopic Anatomy of the Kidney

By the end of this section, you will be able to:

- Distinguish the histological differences between the renal cortex and medulla
- Describe the structure of the filtration membrane
- Identify the major structures and subdivisions of the renal corpuscles, renal tubules, and renal capillaries
- Discuss the function of the peritubular capillaries and vasa recta
- Identify the location of the juxtaglomerular apparatus and describe the cells that line it
- Describe the histology of the proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting ducts

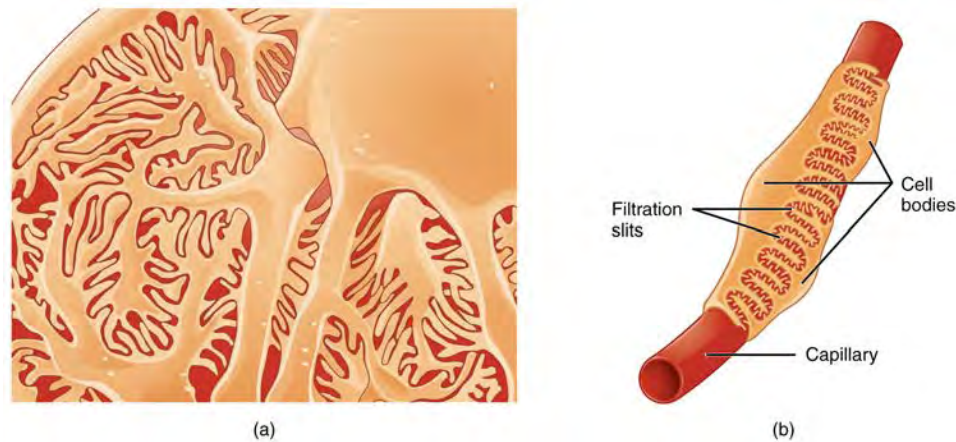
The renal structures that conduct the essential work of the kidney cannot be seen by the naked eye. Only a light or electron microscope can reveal these structures. Even then, serial sections and computer reconstruction are necessary to give us a comprehensive view of the functional anatomy of the nephron and its associated blood vessels.

### Nephrons: The Functional Unit

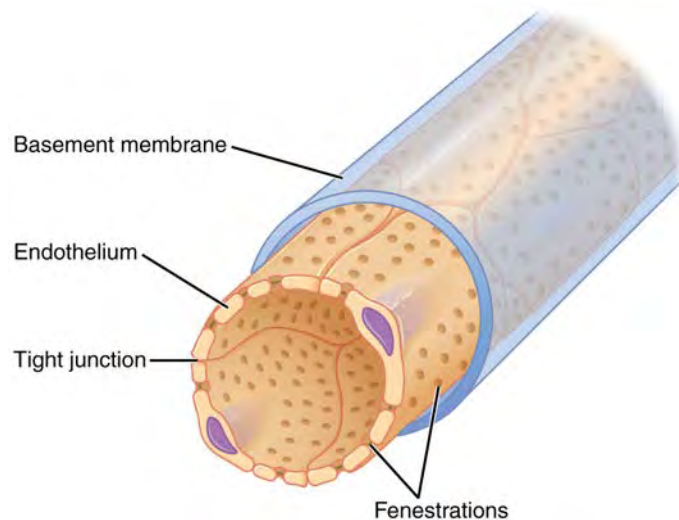
Nephrons take a simple filtrate of the blood and modify it into urine. Many changes take place in the different parts of the nephron before urine is created for disposal. The term **forming urine** will be used hereafter to describe the filtrate as it is modified into true urine. The principle task of the nephron population is to balance the plasma to homeostatic set points and excrete potential toxins in the urine. They do this by accomplishing three principle functions—filtration, reabsorption, and secretion. They also have additional secondary functions that exert control in three areas: blood pressure (via production of **renin**), red blood cell production (via the hormone EPO), and calcium absorption (via conversion of calcidiol into calcitriol, the active form of vitamin D).

#### Renal Corpuscle

As discussed earlier, the renal corpuscle consists of a tuft of capillaries called the glomerulus that is largely surrounded by Bowman's (glomerular) capsule. The glomerulus is a high-pressure capillary bed between afferent and efferent arterioles. Bowman's capsule surrounds the glomerulus to form a lumen, and captures and directs this filtrate to the PCT. The outermost part of Bowman's capsule, the parietal layer, is a simple squamous epithelium. It transitions onto the glomerular capillaries in an intimate embrace to form the visceral layer of the capsule. Here, the cells are not squamous, but uniquely shaped cells ( **podocytes**) extending finger-like arms ( **pedicels**) to cover the glomerular capillaries ( **Figure 25.11**). These projections interdigitate to form **filtration slits**, leaving small gaps between the digits to form a sieve. As blood passes through the glomerulus, 10 to 20 percent of the plasma filters between these sieve-like fingers to be captured by Bowman's capsule and funneled to the PCT. Where the fenestrae (windows) in the glomerular capillaries match the spaces between the podocyte "fingers," the only thing separating the capillary lumen and the lumen of Bowman's capsule is their shared basement membrane ( **Figure 25.12**). These three features comprise what is known as the filtration membrane. This membrane permits very rapid movement of filtrate from capillary to capsule through pores that are only 70 nm in diameter.



**Figure 25.11 Podocytes** Podocytes interdigitate with structures called pedicels and filter substances in a way similar to fenestrations. In (a), the large cell body can be seen at the top right corner, with branches extending from the cell body. The smallest finger-like extensions are the pedicels. Pedicels on one podocyte always interdigitate with the pedicels of another podocyte. (b) This capillary has three podocytes wrapped around it.

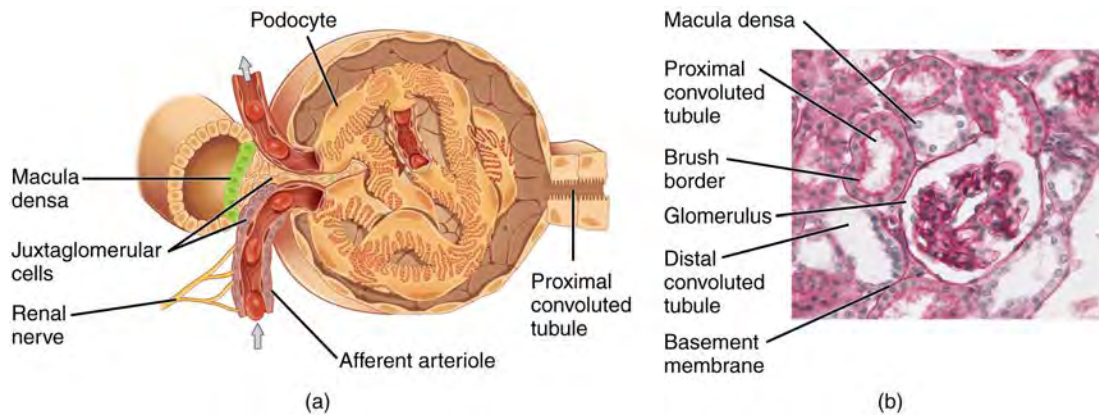


**Figure 25.12 Fenestrated Capillary** Fenestrations allow many substances to diffuse from the blood based primarily on size.

The **fenestrations** prevent filtration of blood cells or large proteins, but allow most other constituents through. These substances cross readily if they are less than 4 nm in size and most pass freely up to 8 nm in size. An additional factor affecting the ability of substances to cross this barrier is their electric charge. The proteins associated with these pores are negatively charged, so they tend to repel negatively charged substances and allow positively charged substances to pass more readily. The basement membrane prevents filtration of medium-to-large proteins such as globulins. There are also **mesangial** cells in the filtration membrane that can contract to help regulate the rate of filtration of the glomerulus. Overall, filtration is regulated by fenestrations in capillary endothelial cells, podocytes with filtration slits, membrane charge, and the basement membrane between capillary cells. The result is the creation of a filtrate that does not contain cells or large proteins, and has a slight predominance of positively charged substances.

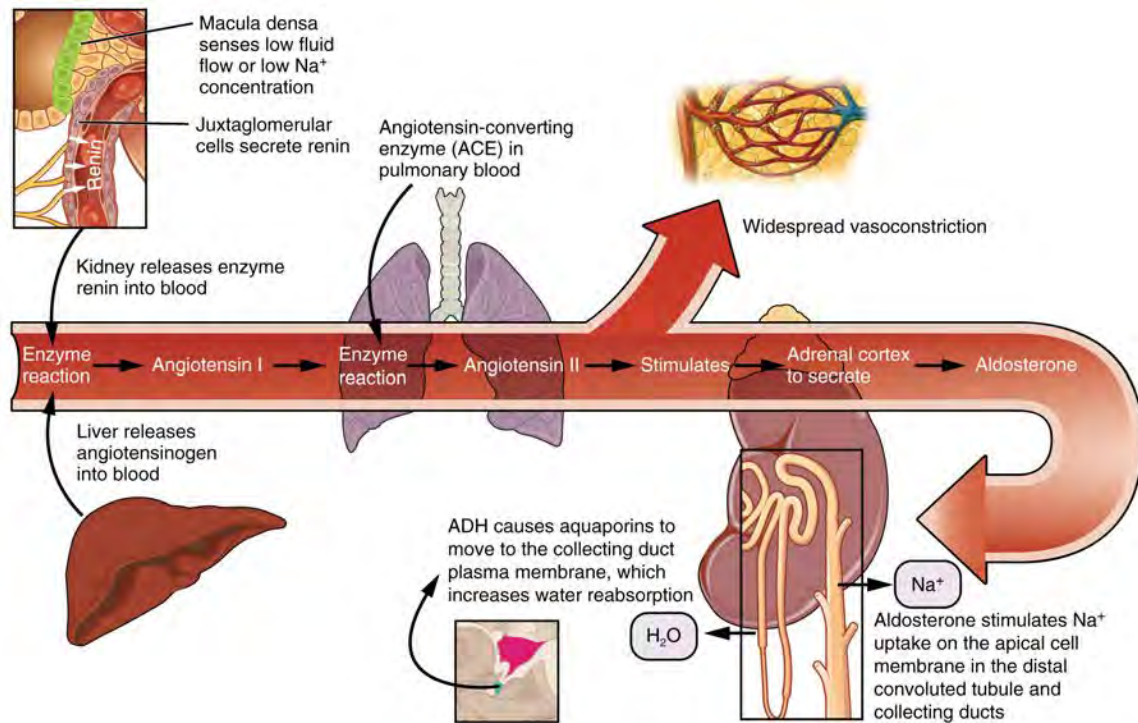
Lying just outside Bowman's capsule and the glomerulus is the **juxtaglomerular apparatus (JGA)** (Figure 25.13). At the juncture where the afferent and efferent arterioles enter and leave Bowman's capsule, the initial part of the distal convoluted tubule (DCT) comes into direct contact with the arterioles. The wall of the DCT at that point forms a part of the JGA known as the **macula densa**. This cluster of cuboidal epithelial cells monitors the fluid composition of fluid flowing through the DCT. In response to the concentration of  $\text{Na}^+$  in the fluid flowing past them, these cells release paracrine signals. They also have a single, nonmotile cilium that responds to the rate of fluid movement in the tubule. The paracrine signals released in

response to changes in flow rate and  $\text{Na}^+$  concentration are adenosine triphosphate (ATP) and adenosine.



**Figure 25.13 Juxtaglomerular Apparatus and Glomerulus** (a) The JGA allows specialized cells to monitor the composition of the fluid in the DCT and adjust the glomerular filtration rate. (b) This micrograph shows the glomerulus and surrounding structures. LM  $\times 1540$ . (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

A second cell type in this apparatus is the **juxtaglomerular cell**. This is a modified, smooth muscle cell lining the afferent arteriole that can contract or relax in response to ATP or adenosine released by the macula densa. Such contraction and relaxation regulate blood flow to the glomerulus. If the osmolarity of the filtrate is too high (hyperosmotic), the juxtaglomerular cells will contract, decreasing the glomerular filtration rate (GFR) so less plasma is filtered, leading to less urine formation and greater retention of fluid. This will ultimately decrease blood osmolarity toward the physiologic norm. If the osmolarity of the filtrate is too low, the juxtaglomerular cells will relax, increasing the GFR and enhancing the loss of water to the urine, causing blood osmolarity to rise. In other words, when osmolarity goes up, filtration and urine formation decrease and water is retained. When osmolarity goes down, filtration and urine formation increase and water is lost by way of the urine. The net result of these opposing actions is to keep the rate of filtration relatively constant. A second function of the macula densa cells is to regulate renin release from the juxtaglomerular cells of the afferent arteriole (**Figure 25.14**). Active renin is a protein comprised of 304 amino acids that cleaves several amino acids from **angiotensinogen** to produce **angiotensin I**. Angiotensin I is not biologically active until converted to angiotensin II by **angiotensin-converting enzyme (ACE)** from the lungs. **Angiotensin II** is a systemic vasoconstrictor that helps to regulate blood pressure by increasing it. Angiotensin II also stimulates the release of the steroid hormone aldosterone from the adrenal cortex. Aldosterone stimulates  $\text{Na}^+$  reabsorption by the kidney, which also results in water retention and increased blood pressure.



**Figure 25.14 Conversion of Angiotensin I to Angiotensin II** The enzyme renin converts the pro-enzyme angiotensin I; the lung-derived enzyme ACE converts angiotensin I into active angiotensin II.

### Proximal Convoluted Tubule (PCT)

Filtered fluid collected by Bowman's capsule enters into the PCT. It is called convoluted due to its tortuous path. Simple cuboidal cells form this tubule with prominent microvilli on the luminal surface, forming a **brush border**. These microvilli create a large surface area to maximize the absorption and secretion of solutes ( $\text{Na}^+$ ,  $\text{Cl}^-$ , glucose, etc.), the most essential function of this portion of the nephron. These cells actively transport ions across their membranes, so they possess a high concentration of mitochondria in order to produce sufficient ATP.

### Loop of Henle

The descending and ascending portions of the loop of Henle (sometimes referred to as the nephron loop) are, of course, just continuations of the same tubule. They run adjacent and parallel to each other after having made a hairpin turn at the deepest point of their descent. The descending loop of Henle consists of an initial short, thick portion and long, thin portion, whereas the ascending loop consists of an initial short, thin portion followed by a long, thick portion. The descending thick portion consists of simple cuboidal epithelium similar to that of the PCT. The descending and ascending thin portions consist of simple squamous epithelium. As you will see later, these are important differences, since different portions of the loop have different permeabilities for solutes and water. The ascending thick portion consists of simple cuboidal epithelium similar to the DCT.

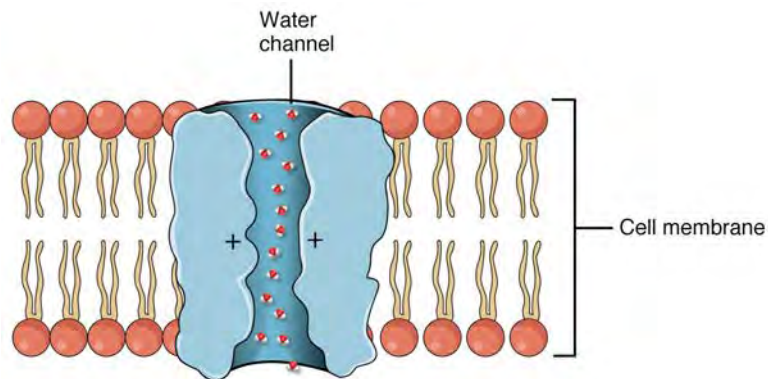
### Distal Convoluted Tubule (DCT)

The DCT, like the PCT, is very tortuous and formed by simple cuboidal epithelium, but it is shorter than the PCT. These cells are not as active as those in the PCT; thus, there are fewer microvilli on the apical surface. However, these cells must also pump ions against their concentration gradient, so you will find of large numbers of mitochondria, although fewer than in the PCT.

### Collecting Ducts

The collecting ducts are continuous with the nephron but not technically part of it. In fact, each duct collects filtrate from several nephrons for final modification. Collecting ducts merge as they descend deeper in the medulla to form about 30 terminal ducts, which empty at a papilla. They are lined with simple squamous epithelium with receptors for ADH. When stimulated by ADH, these cells will insert **aquaporin** channel proteins into their membranes, which as their name suggests, allow water to pass from the duct lumen through the cells and into the interstitial spaces to be recovered by the vasa recta. This process allows for the recovery of large amounts of water from the filtrate back into the blood. In the absence of ADH,

these channels are not inserted, resulting in the excretion of water in the form of dilute urine. Most, if not all, cells of the body contain aquaporin molecules, whose channels are so small that only water can pass. At least 10 types of aquaporins are known in humans, and six of those are found in the kidney. The function of all aquaporins is to allow the movement of water across the lipid-rich, hydrophobic cell membrane (**Figure 25.15**).



**Figure 25.15 Aquaporin Water Channel** Positive charges inside the channel prevent the leakage of electrolytes across the cell membrane, while allowing water to move due to osmosis.

## 25.5 | Physiology of Urine Formation

By the end of this section, you will be able to:

- Describe the hydrostatic and colloid osmotic forces that favor and oppose filtration
- Describe glomerular filtration rate (GFR), state the average value of GFR, and explain how clearance rate can be used to measure GFR
- Predict specific factors that will increase or decrease GFR
- State the percent of the filtrate that is normally reabsorbed and explain why the process of reabsorption is so important
- Calculate daily urine production
- List common symptoms of kidney failure

Having reviewed the anatomy and microanatomy of the urinary system, now is the time to focus on the physiology. You will discover that different parts of the nephron utilize specific processes to produce urine: filtration, reabsorption, and secretion. You will learn how each of these processes works and where they occur along the nephron and collecting ducts. The physiologic goal is to modify the composition of the plasma and, in doing so, produce the waste product urine.

Failure of the renal anatomy and/or physiology can lead suddenly or gradually to renal failure. In this event, a number of symptoms, signs, or laboratory findings point to the diagnosis (**Table 25.3**).

### Symptoms of Kidney Failure

Weakness

Lethargy

Shortness of breath

Widespread edema

Anemia

**Table 25.3**

## Symptoms of Kidney Failure

Metabolic acidosis
Metabolic alkalosis
Heart arrhythmias
Uremia (high urea level in the blood)
Loss of appetite
Fatigue
Excessive urination
Oliguria (too little urine output)

**Table 25.3**

## Glomerular Filtration Rate (GFR)

The volume of filtrate formed by both kidneys per minute is termed the **glomerular filtration rate (GFR)**. The heart pumps about 5 L blood per min under resting conditions. Approximately 20 percent or one liter enters the kidneys to be filtered. On average, this liter results in the production of about 125 mL/min filtrate produced in men (range of 90 to 140 mL/min) and 105 mL/min filtrate produced in women (range of 80 to 125 mL/min). This amount equates to a volume of about 180 L/day in men and 150 L/day in women. Ninety-nine percent of this filtrate is returned to the circulation by reabsorption so that only about 1–2 liters of urine are produced per day (**Table 25.4**).

## Calculating Urine Formation per Day

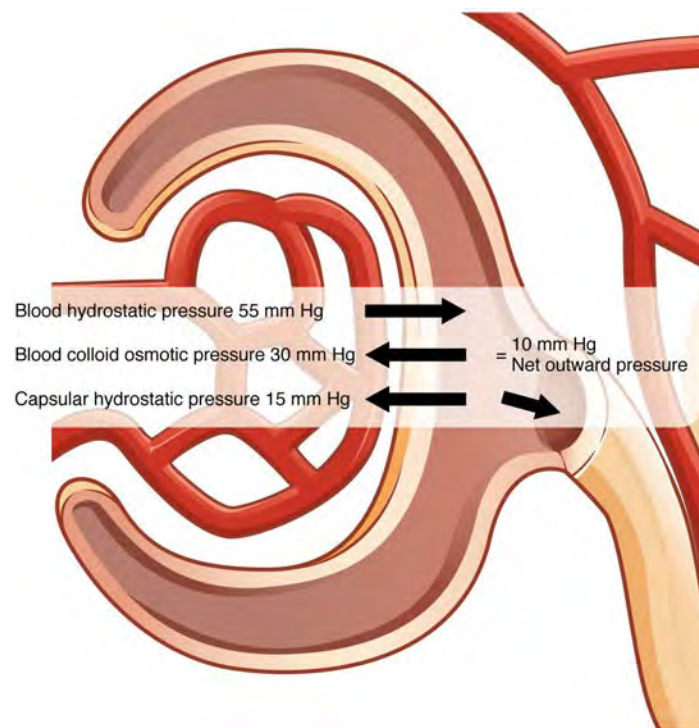
	Flow per minute (mL)	Calculation
Renal blood flow	1050	Cardiac output is about 5000 mL/minute, of which 21 percent flows through the kidney. $5000 \times 0.21 = 1050 \text{ mL blood/min}$
Renal plasma flow	578	Renal plasma flow equals the blood flow per minute times the hematocrit. If a person has a hematocrit of 45, then the renal plasma flow is 55 percent. $1050 \times 0.55 = 578 \text{ mL plasma/min}$
Glomerular filtration rate	110	The GFR is the amount of plasma entering Bowman's capsule per minute. It is the renal plasma flow times the fraction that enters the renal capsule (19 percent). $578 \times 0.19 = 110 \text{ mL filtrate/min}$
Urine	1296 ml/day	The filtrate not recovered by the kidney is the urine that will be eliminated. It is the GFR times the fraction of the filtrate that is not reabsorbed (0.8 percent). $110 \times 0.008 = 0.9 \text{ mL urine /min}$ Multiply urine/min times 60 minutes times 24 hours to get daily urine production. $0.9 \times 60 \times 24 = 1296 \text{ mL/day urine}$

**Table 25.4**

GFR is influenced by the hydrostatic pressure and colloid osmotic pressure on either side of the capillary membrane of the

glomerulus. Recall that filtration occurs as pressure forces fluid and solutes through a semipermeable barrier with the solute movement constrained by particle size. Hydrostatic pressure is the pressure produced by a fluid against a surface. If you have a fluid on both sides of a barrier, both fluids exert a pressure in opposing directions. Net fluid movement will be in the direction of the lower pressure. Osmosis is the movement of solvent (water) across a membrane that is impermeable to a solute in the solution. This creates a pressure, osmotic pressure, which will exist until the solute concentration is the same on both sides of a semipermeable membrane. As long as the concentration differs, water will move. Glomerular filtration occurs when glomerular hydrostatic pressure exceeds the luminal hydrostatic pressure of Bowman's capsule. There is also an opposing force, the osmotic pressure, which is typically higher in the glomerular capillary.

To understand why this is so, look more closely at the microenvironment on either side of the filtration membrane. You will find osmotic pressure exerted by the solutes inside the lumen of the capillary as well as inside of Bowman's capsule. Since the filtration membrane limits the size of particles crossing the membrane, the osmotic pressure inside the glomerular capillary is higher than the osmotic pressure in Bowman's capsule. Recall that cells and the medium-to-large proteins cannot pass between the podocyte processes or through the fenestrations of the capillary endothelial cells. This means that red and white blood cells, platelets, albumins, and other proteins too large to pass through the filter remain in the capillary, creating an average colloid osmotic pressure of 30 mm Hg within the capillary. The absence of proteins in Bowman's space (the lumen within Bowman's capsule) results in an osmotic pressure near zero. Thus, the only pressure moving fluid across the capillary wall into the lumen of Bowman's space is hydrostatic pressure. Hydrostatic (fluid) pressure is sufficient to push water through the membrane despite the osmotic pressure working against it. The sum of all of the influences, both osmotic and hydrostatic, results in a **net filtration pressure (NFP)** of about 10 mm Hg (**Figure 25.16**).



**Figure 25.16 Net Filtration Pressure** The NFP is the sum of osmotic and hydrostatic pressures.

A proper concentration of solutes in the blood is important in maintaining osmotic pressure both in the glomerulus and systemically. There are disorders in which too much protein passes through the filtration slits into the kidney filtrate. This excess protein in the filtrate leads to a deficiency of circulating plasma proteins. In turn, the presence of protein in the urine increases its osmolarity; this holds more water in the filtrate and results in an increase in urine volume. Because there is less circulating protein, principally albumin, the osmotic pressure of the blood falls. Less osmotic pressure pulling water into the capillaries tips the balance towards hydrostatic pressure, which tends to push it out of the capillaries. The net effect is that water is lost from the circulation to interstitial tissues and cells. This “plumps up” the tissues and cells, a condition termed **systemic edema**.

## Net Filtration Pressure (NFP)

NFP determines filtration rates through the kidney. It is determined as follows:

$NFP = \text{Glomerular blood hydrostatic pressure (GBHP)} - [\text{capsular hydrostatic pressure (CHP)} + \text{blood colloid osmotic pressure (BCOP)}] = 10 \text{ mm Hg}$

That is:

$NFP = \text{GBHP} - [\text{CHP} + \text{BCOP}] = 10 \text{ mm Hg}$

Or:

$NFP = 55 - [15 + 30] = 10 \text{ mm Hg}$

As you can see, there is a low net pressure across the filtration membrane. Intuitively, you should realize that minor changes in osmolarity of the blood or changes in capillary blood pressure result in major changes in the amount of filtrate formed at any given point in time. The kidney is able to cope with a wide range of blood pressures. In large part, this is due to the autoregulatory nature of smooth muscle. When you stretch it, it contracts. Thus, when blood pressure goes up, smooth muscle in the afferent capillaries contracts to limit any increase in blood flow and filtration rate. When blood pressure drops, the same capillaries relax to maintain blood flow and filtration rate. The net result is a relatively steady flow of blood into the glomerulus and a relatively steady filtration rate in spite of significant systemic blood pressure changes. Mean arterial blood pressure is calculated by adding 1/3 of the difference between the systolic and diastolic pressures to the diastolic pressure. Therefore, if the blood pressure is 110/80, the difference between systolic and diastolic pressure is 30. One third of this is 10, and when you add this to the diastolic pressure of 80, you arrive at a calculated mean arterial pressure of 90 mm Hg. Therefore, if you use mean arterial pressure for the GBHP in the formula for calculating NFP, you can determine that as long as mean arterial pressure is above approximately 60 mm Hg, the pressure will be adequate to maintain glomerular filtration. Blood pressures below this level will impair renal function and cause systemic disorders that are severe enough to threaten survival. This condition is called shock.

Determination of the GFR is one of the tools used to assess the kidney's excretory function. This is more than just an academic exercise. Since many drugs are excreted in the urine, a decline in renal function can lead to toxic accumulations. Additionally, administration of appropriate drug dosages for those drugs primarily excreted by the kidney requires an accurate assessment of GFR. GFR can be estimated closely by intravenous administration of **inulin**. Inulin is a plant polysaccharide that is neither reabsorbed nor secreted by the kidney. Its appearance in the urine is directly proportional to the rate at which it is filtered by the renal corpuscle. However, since measuring inulin clearance is cumbersome in the clinical setting, most often, the GFR is estimated by measuring naturally occurring creatinine, a protein-derived molecule produced by muscle metabolism that is not reabsorbed and only slightly secreted by the nephron.

## 25.6 | Tubular Reabsorption

By the end of this section, you will be able to:

- List specific transport mechanisms occurring in different parts of the nephron, including active transport, osmosis, facilitated diffusion, and passive electrochemical gradients
- List the different membrane proteins of the nephron, including channels, transporters, and ATPase pumps
- Compare and contrast passive and active tubular reabsorption
- Explain why the differential permeability or impermeability of specific sections of the nephron tubules is necessary for urine formation
- Describe how and where water, organic compounds, and ions are reabsorbed in the nephron
- Explain the role of the loop of Henle, the vasa recta, and the countercurrent multiplication mechanisms in the concentration of urine
- List the locations in the nephron where tubular secretion occurs

With up to 180 liters per day passing through the nephrons of the kidney, it is quite obvious that most of that fluid and its contents must be reabsorbed. That recovery occurs in the PCT, loop of Henle, DCT, and the collecting ducts (**Table 25.5** and **Figure 25.17**). Various portions of the nephron differ in their capacity to reabsorb water and specific solutes. While much of the reabsorption and secretion occur passively based on concentration gradients, the amount of water that is reabsorbed or lost is tightly regulated. This control is exerted directly by ADH and aldosterone, and indirectly by renin. Most water is recovered in the PCT, loop of Henle, and DCT. About 10 percent (about 18 L) reaches the collecting ducts. The collecting ducts, under the influence of ADH, can recover almost all of the water passing through them, in cases of dehydration, or almost none of the water, in cases of over-hydration.

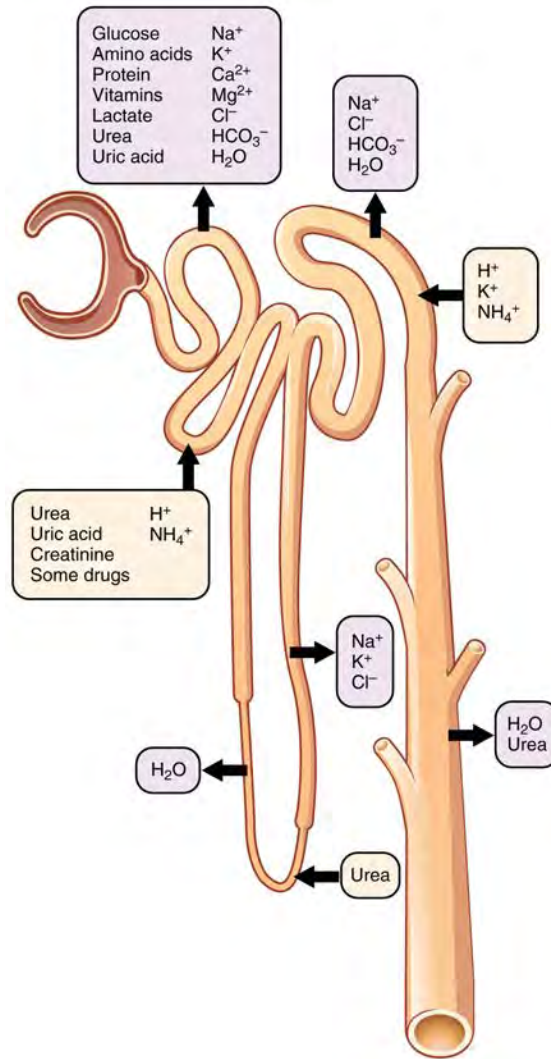


Figure 25.17 Locations of Secretion and Reabsorption in the Nephron

### Substances Secreted or Reabsorbed in the Nephron and Their Locations

Substance	PCT	Loop of Henle	DCT	Collecting ducts
Glucose	Almost 100 percent reabsorbed; secondary active transport with Na <sup>+</sup>			
Oligopeptides, proteins, amino acids	Almost 100 percent reabsorbed; symport with Na <sup>+</sup>			
Vitamins	Reabsorbed			
Lactate	Reabsorbed			
Creatinine	Secreted			

Table 25.5

## Substances Secreted or Reabsorbed in the Nephron and Their Locations

Substance	PCT	Loop of Henle	DCT	Collecting ducts
Urea	50 percent reabsorbed by diffusion; also secreted	Secretion, diffusion in descending limb		Reabsorption in medullary collecting ducts; diffusion
Sodium	65 percent actively reabsorbed	25 percent reabsorbed in thick ascending limb; active transport	5 percent reabsorbed; active	5 percent reabsorbed, stimulated by aldosterone; active
Chloride	Reabsorbed, symport with $\text{Na}^+$ , diffusion	Reabsorbed in thin and thick ascending limb; diffusion in ascending limb	Reabsorbed; diffusion	Reabsorbed; symport
Water	67 percent reabsorbed osmotically with solutes	15 percent reabsorbed in descending limb; osmosis	8 percent reabsorbed if ADH; osmosis	Variable amounts reabsorbed, controlled by ADH, osmosis
Bicarbonate	80–90 percent symport reabsorption with $\text{Na}^+$	Reabsorbed, symport with $\text{Na}^+$ and antiport with $\text{Cl}^-$ ; in ascending limb		Reabsorbed antiport with $\text{Cl}^-$
$\text{H}^+$	Secreted; diffusion		Secreted; active	Secreted; active
$\text{NH}_4^+$	Secreted; diffusion		Secreted; diffusion	Secreted; diffusion
$\text{HCO}_3^-$	Reabsorbed; diffusion	Reabsorbed; diffusion in ascending limb	Reabsorbed; diffusion	Reabsorbed; antiport with $\text{Na}^+$
Some drugs	Secreted		Secreted; active	Secreted; active
Potassium	65 percent reabsorbed; diffusion	20 percent reabsorbed in thick ascending limb; symport	Secreted; active	Secretion controlled by aldosterone; active
Calcium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion		Reabsorbed if parathyroid hormone present; active
Magnesium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion	Reabsorbed	
Phosphate	85 percent reabsorbed, inhibited by parathyroid hormone, diffusion		Reabsorbed; diffusion	

**Table 25.5**

## Mechanisms of Recovery

Mechanisms by which substances move across membranes for reabsorption or secretion include active transport, diffusion, facilitated diffusion, secondary active transport, and osmosis. These were discussed in an earlier chapter, and you may wish to review them.

Active transport utilizes energy, usually the energy found in a phosphate bond of ATP, to move a substance across a membrane from a low to a high concentration. It is very specific and must have an appropriately shaped receptor for the substance to be transported. An example would be the active transport of  $\text{Na}^+$  out of a cell and  $\text{K}^+$  into a cell by the  $\text{Na}^+/\text{K}^+$

pump. Both ions are moved in opposite directions from a lower to a higher concentration.

Simple diffusion moves a substance from a higher to a lower concentration down its concentration gradient. It requires no energy and only needs to be soluble.

Facilitated diffusion is similar to diffusion in that it moves a substance down its concentration gradient. The difference is that it requires specific membrane receptors or channel proteins for movement. The movement of glucose and, in certain situations,  $\text{Na}^+$  ions, is an example of facilitated diffusion. In some cases of mediated transport, two different substances share the same channel protein port; these mechanisms are described by the terms symport and antiport.

Symport mechanisms move two or more substances in the same direction at the same time, whereas antiport mechanisms move two or more substances in opposite directions across the cell membrane. Both mechanisms may utilize concentration gradients maintained by ATP pumps. As described previously, when active transport powers the transport of another substance in this way, it is called “secondary active transport.” Glucose reabsorption in the kidneys is by secondary active transport.  $\text{Na}^+/\text{K}^+$  ATPases on the basal membrane of a tubular cell constantly pump  $\text{Na}^+$  out of the cell, maintaining a strong electrochemical gradient for  $\text{Na}^+$  to move into the cell from the tubular lumen. On the luminal (apical) surface, a  $\text{Na}^+$ /glucose symport protein assists both  $\text{Na}^+$  and glucose movement into the cell. The cotransporter moves glucose into the cell against its concentration gradient as  $\text{Na}^+$  moves down the electrochemical gradient created by the basal membranes  $\text{Na}^+/\text{K}^+$  ATPases. The glucose molecule then diffuses across the basal membrane by facilitated diffusion into the interstitial space and from there into peritubular capillaries.

Most of the  $\text{Ca}^{++}$ ,  $\text{Na}^+$ , glucose, and amino acids must be reabsorbed by the nephron to maintain homeostatic plasma concentrations. Other substances, such as urea,  $\text{K}^+$ , ammonia ( $\text{NH}_3$ ), creatinine, and some drugs are secreted into the filtrate as waste products. Acid–base balance is maintained through actions of the lungs and kidneys: The lungs rid the body of  $\text{H}^+$ , whereas the kidneys secrete or reabsorb  $\text{H}^+$  and  $\text{HCO}_3^-$  (Table 25.6). In the case of urea, about 50 percent is passively reabsorbed by the PCT. More is recovered by in the collecting ducts as needed. ADH induces the insertion of urea transporters and aquaporin channel proteins.

### Substances Filtered and Reabsorbed by the Kidney per 24 Hours

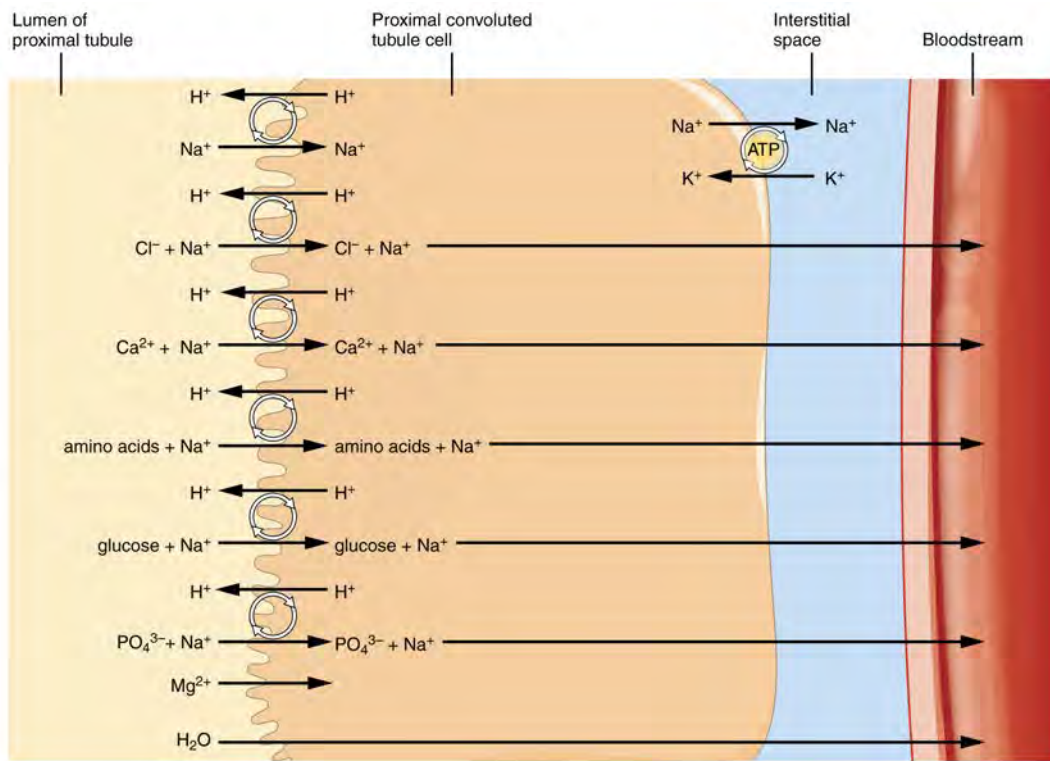
Substance	Amount filtered (grams)	Amount reabsorbed (grams)	Amount in urine (grams)
Water	180 L	179 L	1 L
Proteins	10–20	10–20	0
Chlorine	630	625	5
Sodium	540	537	3
Bicarbonate	300	299.7	0.3
Glucose	180	180	0
Urea	53	28	25
Potassium	28	24	4
Uric acid	8.5	7.7	0.8
Creatinine	1.4	0	1.4

Table 25.6

### Reabsorption and Secretion in the PCT

The renal corpuscle filters the blood to create a filtrate that differs from blood mainly in the absence of cells and large proteins. From this point to the ends of the collecting ducts, the filtrate or forming urine is undergoing modification through secretion and reabsorption before true urine is produced. The first point at which the forming urine is modified is in the PCT. Here, some substances are reabsorbed, whereas others are secreted. Note the use of the term “reabsorbed.” All of these substances were “absorbed” in the digestive tract—99 percent of the water and most of the solutes filtered by the nephron must be reabsorbed. Water and substances that are reabsorbed are returned to the circulation by the peritubular

and vasa recta capillaries. It is important to understand the difference between the glomerulus and the peritubular and vasa recta capillaries. The glomerulus has a relatively high pressure inside its capillaries and can sustain this by dilating the afferent arteriole while constricting the efferent arteriole. This assures adequate filtration pressure even as the systemic blood pressure varies. Movement of water into the peritubular capillaries and vasa recta will be influenced primarily by osmolarity and concentration gradients. Sodium is actively pumped out of the PCT into the interstitial spaces between cells and diffuses down its concentration gradient into the peritubular capillary. As it does so, water will follow passively to maintain an isotonic fluid environment inside the capillary. This is called obligatory water reabsorption, because water is “obliged” to follow the  $\text{Na}^+$  (Figure 25.18).



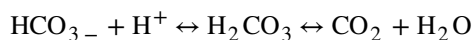
**Figure 25.18** Substances Reabsorbed and Secreted by the PCT

More substances move across the membranes of the PCT than any other portion of the nephron. Many of these substances (amino acids and glucose) use symport mechanisms for transport along with  $\text{Na}^+$ . Antiport, active transport, diffusion, and facilitated diffusion are additional mechanisms by which substances are moved from one side of a membrane to the other. Recall that cells have two surfaces: apical and basal. The apical surface is the one facing the lumen or open space of a cavity or tube, in this case, the inside of the PCT. The basal surface of the cell faces the connective tissue base to which the cell attaches (basement membrane) or the cell membrane closer to the basement membrane if there is a stratified layer of cells. In the PCT, there is a single layer of simple cuboidal endothelial cells against the basement membrane. The numbers and particular types of pumps and channels vary between the apical and basilar surfaces. A few of the substances that are transported with  $\text{Na}^+$  (symport mechanism) on the apical membrane include  $\text{Cl}^-$ ,  $\text{Ca}^{++}$ , amino acids, glucose, and  $\text{PO}_4^{3-}$ . Sodium is actively exchanged for  $\text{K}^+$  using ATP on the basal membrane. Most of the substances transported by a symport mechanism on the apical membrane are transported by facilitated diffusion on the basal membrane. At least three ions,  $\text{K}^+$ ,  $\text{Ca}^{++}$ , and  $\text{Mg}^{++}$ , diffuse laterally between adjacent cell membranes (transcellular).

About 67 percent of the water,  $\text{Na}^+$ , and  $\text{K}^+$  entering the nephron is reabsorbed in the PCT and returned to the circulation. Almost 100 percent of glucose, amino acids, and other organic substances such as vitamins are normally recovered here. Some glucose may appear in the urine if circulating glucose levels are high enough that all the glucose transporters in the PCT are saturated, so that their capacity to move glucose is exceeded (transport maximum, or  $T_m$ ). In men, the maximum amount of glucose that can be recovered is about 375 mg/min, whereas in women, it is about 300 mg/min. This recovery rate translates to an arterial concentration of about 200 mg/dL. Though an exceptionally high sugar intake might cause sugar to appear briefly in the urine, the appearance of **glycosuria** usually points to type I or II diabetes mellitus. The transport of

glucose from the lumen of the PCT to the interstitial space is similar to the way it is absorbed by the small intestine. Both glucose and  $\text{Na}^+$  bind simultaneously to the same symport proteins on the apical surface of the cell to be transported in the same direction, toward the interstitial space. Sodium moves down its electrochemical and concentration gradient into the cell and takes glucose with it.  $\text{Na}^+$  is then actively pumped out of the cell at the basal surface of the cell into the interstitial space. Glucose leaves the cell to enter the interstitial space by facilitated diffusion. The energy to move glucose comes from the  $\text{Na}^+/\text{K}^+$  ATPase that pumps  $\text{Na}^+$  out of the cell on the basal surface. Fifty percent of  $\text{Cl}^-$  and variable quantities of  $\text{Ca}^{++}$ ,  $\text{Mg}^{++}$ , and  $\text{HPO}_4^{2-}$  are also recovered in the PCT.

Recovery of bicarbonate ( $\text{HCO}_3^-$ ) is vital to the maintenance of acid–base balance, since it is a very powerful and fast-acting buffer. An important enzyme is used to catalyze this mechanism: carbonic anhydrase (CA). This same enzyme and reaction is used in red blood cells in the transportation of  $\text{CO}_2$ , in the stomach to produce hydrochloric acid, and in the pancreas to produce  $\text{HCO}_3^-$  to buffer acidic chyme from the stomach. In the kidney, most of the CA is located within the cell, but a small amount is bound to the brush border of the membrane on the apical surface of the cell. In the lumen of the PCT,  $\text{HCO}_3^-$  combines with hydrogen ions to form carbonic acid ( $\text{H}_2\text{CO}_3$ ). This is enzymatically catalyzed into  $\text{CO}_2$  and water, which diffuse across the apical membrane into the cell. Water can move osmotically across the lipid bilayer membrane due to the presence of aquaporin water channels. Inside the cell, the reverse reaction occurs to produce bicarbonate ions ( $\text{HCO}_3^-$ ). These bicarbonate ions are cotransported with  $\text{Na}^+$  across the basal membrane to the interstitial space around the PCT (Figure 25.19). At the same time this is occurring, a  $\text{Na}^+/\text{H}^+$  antiporter excretes  $\text{H}^+$  into the lumen, while it recovers  $\text{Na}^+$ . Note how the hydrogen ion is recycled so that bicarbonate can be recovered. Also, note that a  $\text{Na}^+$  gradient is created by the  $\text{Na}^+/\text{K}^+$  pump.



The significant recovery of solutes from the PCT lumen to the interstitial space creates an osmotic gradient that promotes water recovery. As noted before, water moves through channels created by the aquaporin proteins. These proteins are found in all cells in varying amounts and help regulate water movement across membranes and through cells by creating a passageway across the hydrophobic lipid bilayer membrane. Changing the number of aquaporin proteins in membranes of the collecting ducts also helps to regulate the osmolarity of the blood. The movement of many positively charged ions also creates an electrochemical gradient. This charge promotes the movement of negative ions toward the interstitial spaces and the movement of positive ions toward the lumen.

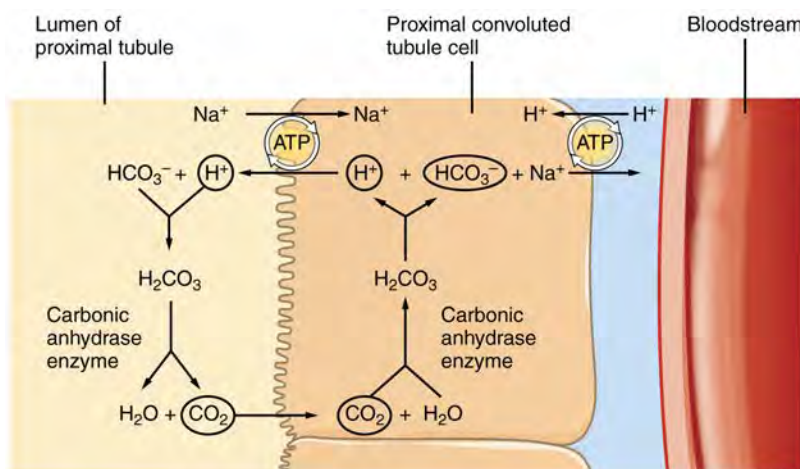


Figure 25.19 Reabsorption of Bicarbonate from the PCT

## Reabsorption and Secretion in the Loop of Henle

The loop of Henle consists of two sections: thick and thin descending and thin and thick ascending sections. The loops of cortical nephrons do not extend into the renal medulla very far, if at all. Juxtamedullary nephrons have loops that extend variable distances, some very deep into the medulla. The descending and ascending portions of the loop are highly specialized to enable recovery of much of the  $\text{Na}^+$  and water that were filtered by the glomerulus. As the forming urine moves through the loop, the osmolarity will change from isosmotic with blood (about 278–300 mOsmol/kg) to both a very

hypertonic solution of about 1200 mOsmol/kg and a very hypotonic solution of about 100 mOsmol/kg. These changes are accomplished by osmosis in the descending limb and active transport in the ascending limb. Solutes and water recovered from these loops are returned to the circulation by way of the vasa recta.

### Descending Loop

The majority of the descending loop is comprised of simple squamous epithelial cells; to simplify the function of the loop, this discussion focuses on these cells. These membranes have permanent aquaporin channel proteins that allow unrestricted movement of water from the descending loop into the surrounding interstitium as osmolarity increases from about 300 mOsmol/kg to about 1200 mOsmol/kg. This increase results in reabsorption of up to 15 percent of the water entering the nephron. Modest amounts of urea,  $\text{Na}^+$ , and other ions are also recovered here.

Most of the solutes that were filtered in the glomerulus have now been recovered along with a majority of water, about 82 percent. As the forming urine enters the ascending loop, major adjustments will be made to the concentration of solutes to create what you perceive as urine.

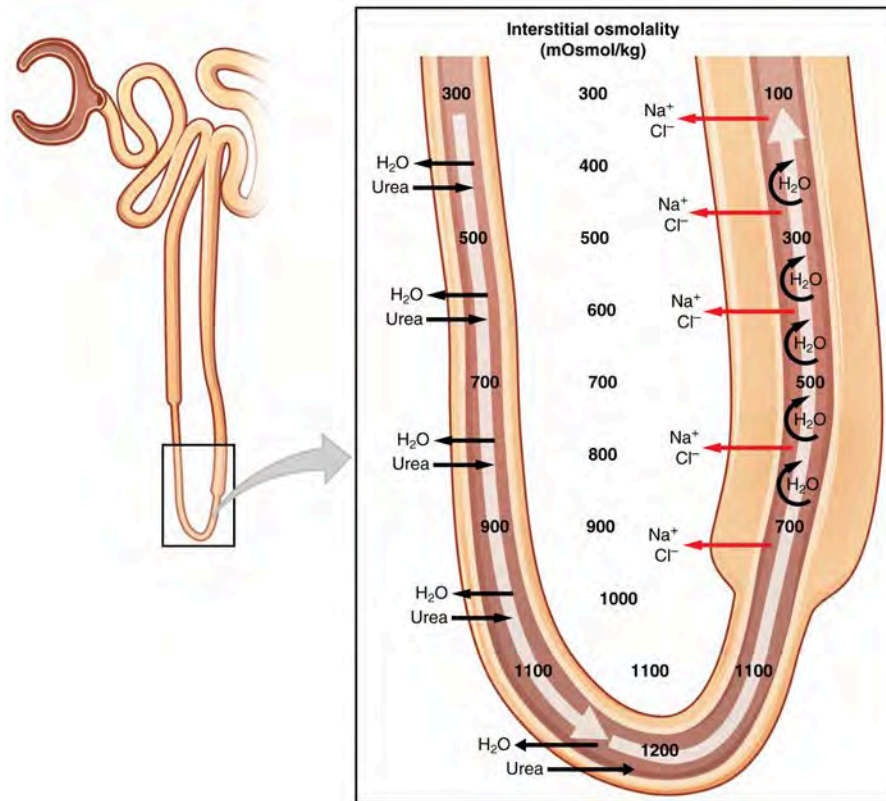
### Ascending Loop

The ascending loop is made of very short thin and longer thick portions. Once again, to simplify the function, this section only considers the thick portion. The thick portion is lined with simple cuboidal epithelium without a brush border. It is completely impermeable to water due to the absence of aquaporin proteins, but ions, mainly  $\text{Na}^+$  and  $\text{Cl}^-$ , are actively reabsorbed by a cotransport system. This has two significant effects: Removal of NaCl while retaining water leads to a hyposmotic filtrate by the time it reaches the DCT; pumping NaCl into the interstitial space contributes to the hyperosmotic environment in the kidney medulla.

The  $\text{Na}^+/\text{K}^+$  ATPase pumps in the basal membrane create an electrochemical gradient, allowing reabsorption of  $\text{Cl}^-$  by  $\text{Na}^+/\text{Cl}^-$  symporters in the apical membrane. At the same time that  $\text{Na}^+$  is actively pumped from the basal side of the cell into the interstitial fluid,  $\text{Cl}^-$  follows the  $\text{Na}^+$  from the lumen into the interstitial fluid by a paracellular route between cells through **leaky tight junctions**. These are found between cells of the ascending loop, where they allow certain solutes to move according to their concentration gradient. Most of the  $\text{K}^+$  that enters the cell via symporters returns to the lumen (down its concentration gradient) through leaky channels in the apical membrane. Note the environment now created in the interstitial space: With the “back door exiting”  $\text{K}^+$ , there is one  $\text{Na}^+$  and two  $\text{Cl}^-$  ions left in the interstitium surrounding the ascending loop. Therefore, in comparison to the lumen of the loop, the interstitial space is now a negatively charged environment. This negative charge attracts cations ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$ , and  $\text{Mg}^{++}$ ) from the lumen via a paracellular route to the interstitial space and vasa recta.

### Countercurrent Multiplier System

The structure of the loop of Henle and associated vasa recta create a **countercurrent multiplier system** (Figure 25.20). The countercurrent term comes from the fact that the descending and ascending loops are next to each other and their fluid flows in opposite directions (countercurrent). The multiplier term is due to the action of solute pumps that increase (multiply) the concentrations of urea and  $\text{Na}^+$  deep in the medulla.



**Figure 25.20 Countercurrent Multiplier System**

As discussed above, the ascending loop actively reabsorbs  $\text{NaCl}$  out of the forming urine into the interstitial spaces. In addition, collecting ducts have urea pumps that actively pump urea into the interstitial spaces. This results in the recovery of  $\text{NaCl}$  to the circulation via the vasa recta and creates a high osmolar environment in the depths of the medulla.

Ammonia ( $\text{NH}_3$ ) is a toxic byproduct of protein metabolism. It is formed as amino acids are deaminated by liver hepatocytes. That means that the amine group,  $\text{NH}_2$ , is removed from amino acids as they are broken down. Most of the resulting ammonia is converted into urea by liver hepatocytes. Urea is not only less toxic but is utilized to aid in the recovery of water by the loop of Henle and collecting ducts. At the same time that water is freely diffusing out of the descending loop through aquaporin channels into the interstitial spaces of the medulla, urea freely diffuses into the lumen of the descending loop as it descends deeper into the medulla, much of it to be reabsorbed from the forming urine when it reaches the collecting duct. Thus, the movement of  $\text{Na}^+$  and urea into the interstitial spaces by these mechanisms creates the hyperosmotic environment of the medulla. The net result of this countercurrent multiplier system is to recover both water and  $\text{Na}^+$  in the circulation.

The amino acid glutamine can be deaminated by the kidney. As  $\text{NH}_2$  from the amino acid is converted into  $\text{NH}_3$  and pumped into the lumen of the PCT,  $\text{Na}^+$  and  $\text{HCO}_3^-$  are excreted into the interstitial fluid of the renal pyramid via a symport mechanism. When this process occurs in the cells of the PCT, the added benefit is a net loss of a hydrogen ion (complexed to ammonia to form the weak acid  $\text{NH}_4^+$ ) in the urine and a gain of a bicarbonate ion ( $\text{HCO}_3^-$ ) in the blood. Ammonia and bicarbonate are exchanged in a one-to-one ratio. This exchange is yet another means by which the body can buffer and excrete acid. The presence of aquaporin channels in the descending loop allows prodigious quantities of water to leave the loop and enter the hyperosmolar interstitium of the pyramid, where it is returned to the circulation by the vasa recta. As the loop turns to become the ascending loop, there is an absence of aquaporin channels, so water cannot leave the loop. However, in the basal membrane of cells of the thick ascending loop, ATPase pumps actively remove  $\text{Na}^+$  from the cell. A  $\text{Na}^+/\text{K}^+/\text{2Cl}^-$  symporter in the apical membrane passively allows these ions to enter the cell cytoplasm from the lumen of the loop down a concentration gradient created by the pump. This mechanism works to dilute the fluid of the ascending loop ultimately to approximately 50–100 mOsmol/L.

At the transition from the DCT to the collecting duct, about 20 percent of the original water is still present and about 10

percent of the sodium. If no other mechanism for water reabsorption existed, about 20–25 liters of urine would be produced. Now consider what is happening in the adjacent capillaries, the vasa recta. They are recovering both solutes and water at a rate that preserves the countercurrent multiplier system. In general, blood flows slowly in capillaries to allow time for exchange of nutrients and wastes. In the vasa recta particularly, this rate of flow is important for two additional reasons. The flow must be slow to allow blood cells to lose and regain water without either crenating or bursting. Second, a rapid flow would remove too much  $\text{Na}^+$  and urea, destroying the osmolar gradient that is necessary for the recovery of solutes and water. Thus, by flowing slowly to preserve the countercurrent mechanism, as the vasa recta descend,  $\text{Na}^+$  and urea are freely able to enter the capillary, while water freely leaves; as they ascend,  $\text{Na}^+$  and urea are secreted into the surrounding medulla, while water reenters and is removed.

## Interactive LINK



Watch this [video \(http://openstaxcollege.org/l/multiplier\)](http://openstaxcollege.org/l/multiplier) to learn about the countercurrent multiplier system.

## Reabsorption and Secretion in the Distal Convoluted Tubule

Approximately 80 percent of filtered water has been recovered by the time the dilute forming urine enters the DCT. The DCT will recover another 10–15 percent before the forming urine enters the collecting ducts. Aldosterone increases the amount of  $\text{Na}^+/\text{K}^+$  ATPase in the basal membrane of the DCT and collecting duct. The movement of  $\text{Na}^+$  out of the lumen of the collecting duct creates a negative charge that promotes the movement of  $\text{Cl}^-$  out of the lumen into the interstitial space by a paracellular route across tight junctions. Peritubular capillaries receive the solutes and water, returning them to the circulation.

Cells of the DCT also recover  $\text{Ca}^{++}$  from the filtrate. Receptors for parathyroid hormone (PTH) are found in DCT cells and when bound to PTH, induce the insertion of calcium channels on their luminal surface. The channels enhance  $\text{Ca}^{++}$  recovery from the forming urine. In addition, as  $\text{Na}^+$  is pumped out of the cell, the resulting electrochemical gradient attracts  $\text{Ca}^{++}$  into the cell. Finally, calcitriol (1,25 dihydroxyvitamin D, the active form of vitamin D) is very important for calcium recovery. It induces the production of calcium-binding proteins that transport  $\text{Ca}^{++}$  into the cell. These binding proteins are also important for the movement of calcium inside the cell and aid in exocytosis of calcium across the basolateral membrane. Any  $\text{Ca}^{++}$  not reabsorbed at this point is lost in the urine.

## Collecting Ducts and Recovery of Water

Solutes move across the membranes of the collecting ducts, which contain two distinct cell types, principal cells and intercalated cells. A **principal cell** possesses channels for the recovery or loss of sodium and potassium. An **intercalated cell** secretes or absorbs acid or bicarbonate. As in other portions of the nephron, there is an array of micromachines (pumps and channels) on display in the membranes of these cells.

Regulation of urine volume and osmolarity are major functions of the collecting ducts. By varying the amount of water that is recovered, the collecting ducts play a major role in maintaining the body's normal osmolarity. If the blood becomes hyperosmotic, the collecting ducts recover more water to dilute the blood; if the blood becomes hyposmotic, the collecting ducts recover less of the water, leading to concentration of the blood. Another way of saying this is: If plasma osmolarity rises, more water is recovered and urine volume decreases; if plasma osmolarity decreases, less water is recovered and urine volume increases. This function is regulated by the posterior pituitary hormone ADH (vasopressin). With mild dehydration, plasma osmolarity rises slightly. This increase is detected by osmoreceptors in the hypothalamus, which stimulates the release of ADH from the posterior pituitary. If plasma osmolarity decreases slightly, the opposite occurs.

When stimulated by ADH, aquaporin channels are inserted into the apical membrane of principal cells, which line the collecting ducts. As the ducts descend through the medulla, the osmolarity surrounding them increases (due to the countercurrent mechanisms described above). If aquaporin water channels are present, water will be osmotically pulled from the collecting duct into the surrounding interstitial space and into the peritubular capillaries. Therefore, the final urine will be more concentrated. If less ADH is secreted, fewer aquaporin channels are inserted and less water is recovered, resulting in dilute urine. By altering the number of aquaporin channels, the volume of water recovered or lost is altered. This, in turn, regulates the blood osmolarity, blood pressure, and osmolarity of the urine.

As  $\text{Na}^+$  is pumped from the forming urine, water is passively recaptured for the circulation; this preservation of vascular volume is critically important for the maintenance of a normal blood pressure. Aldosterone is secreted by the adrenal cortex in response to angiotensin II stimulation. As an extremely potent vasoconstrictor, angiotensin II functions immediately to increase blood pressure. By also stimulating aldosterone production, it provides a longer-lasting mechanism to support blood pressure by maintaining vascular volume (water recovery).

In addition to receptors for ADH, principal cells have receptors for the steroid hormone aldosterone. While ADH is primarily involved in the regulation of water recovery, aldosterone regulates  $\text{Na}^+$  recovery. Aldosterone stimulates principal cells to manufacture luminal  $\text{Na}^+$  and  $\text{K}^+$  channels as well as  $\text{Na}^+/\text{K}^+$  ATPase pumps on the basal membrane of the cells. When aldosterone output increases, more  $\text{Na}^+$  is recovered from the forming urine and water follows the  $\text{Na}^+$  passively. As the pump recovers  $\text{Na}^+$  for the body, it is also pumping  $\text{K}^+$  into the forming urine, since the pump moves  $\text{K}^+$  in the opposite direction. When aldosterone decreases, more  $\text{Na}^+$  remains in the forming urine and more  $\text{K}^+$  is recovered in the circulation. Symport channels move  $\text{Na}^+$  and  $\text{Cl}^-$  together. Still other channels in the principal cells secrete  $\text{K}^+$  into the collecting duct in direct proportion to the recovery of  $\text{Na}^+$ .

Intercalated cells play significant roles in regulating blood pH. Intercalated cells reabsorb  $\text{K}^+$  and  $\text{HCO}_3^-$  while secreting  $\text{H}^+$ . This function lowers the acidity of the plasma while increasing the acidity of the urine.

## 25.7 | Regulation of Renal Blood Flow

By the end of this section, you will be able to:

- Describe the myogenic and tubuloglomerular feedback mechanisms and explain how they affect urine volume and composition
- Describe the function of the juxtaglomerular apparatus

It is vital that the flow of blood through the kidney be at a suitable rate to allow for filtration. This rate determines how much solute is retained or discarded, how much water is retained or discarded, and ultimately, the osmolarity of blood and the blood pressure of the body.

### Sympathetic Nerves

The kidneys are innervated by the sympathetic neurons of the autonomic nervous system via the celiac plexus and splanchnic nerves. Reduction of sympathetic stimulation results in vasodilation and increased blood flow through the kidneys during resting conditions. When the frequency of action potentials increases, the arteriolar smooth muscle constricts (vasoconstriction), resulting in diminished glomerular flow, so less filtration occurs. Under conditions of stress, sympathetic nervous activity increases, resulting in the direct vasoconstriction of afferent arterioles (norepinephrine effect) as well as stimulation of the adrenal medulla. The adrenal medulla, in turn, produces a generalized vasoconstriction through the release of epinephrine. This includes vasoconstriction of the afferent arterioles, further reducing the volume of blood flowing through the kidneys. This process redirects blood to other organs with more immediate needs. If blood pressure falls, the sympathetic nerves will also stimulate the release of renin. Additional renin increases production of the powerful vasoconstrictor angiotensin II. Angiotensin II, as discussed above, will also stimulate aldosterone production to augment blood volume through retention of more  $\text{Na}^+$  and water. Only a 10 mm Hg pressure differential across the glomerulus is required for normal GFR, so very small changes in afferent arterial pressure significantly increase or decrease GFR.

### Autoregulation

The kidneys are very effective at regulating the rate of blood flow over a wide range of blood pressures. Your blood pressure will decrease when you are relaxed or sleeping. It will increase when exercising. Yet, despite these changes, the filtration

rate through the kidney will change very little. This is due to two internal autoregulatory mechanisms that operate without outside influence: the myogenic mechanism and the tubuloglomerular feedback mechanism.

### Arteriole Myogenic Mechanism

The **myogenic mechanism** regulating blood flow within the kidney depends upon a characteristic shared by most smooth muscle cells of the body. When you stretch a smooth muscle cell, it contracts; when you stop, it relaxes, restoring its resting length. This mechanism works in the afferent arteriole that supplies the glomerulus. When blood pressure increases, smooth muscle cells in the wall of the arteriole are stretched and respond by contracting to resist the pressure, resulting in little change in flow. When blood pressure drops, the same smooth muscle cells relax to lower resistance, allowing a continued even flow of blood.

### Tubuloglomerular Feedback

The **tubuloglomerular feedback** mechanism involves the JGA and a paracrine signaling mechanism utilizing ATP, adenosine, and nitric oxide (NO). This mechanism stimulates either contraction or relaxation of afferent arteriolar smooth muscle cells (**Table 25.7**). Recall that the DCT is in intimate contact with the afferent and efferent arterioles of the glomerulus. Specialized macula densa cells in this segment of the tubule respond to changes in the fluid flow rate and  $\text{Na}^+$  concentration. As GFR increases, there is less time for  $\text{NaCl}$  to be reabsorbed in the PCT, resulting in higher osmolarity in the filtrate. The increased fluid movement more strongly deflects single nonmotile cilia on macula densa cells. This increased osmolarity of the forming urine, and the greater flow rate within the DCT, activates macula densa cells to respond by releasing ATP and adenosine (a metabolite of ATP). ATP and adenosine act locally as paracrine factors to stimulate the myogenic juxtaglomerular cells of the afferent arteriole to constrict, slowing blood flow and reducing GFR. Conversely, when GFR decreases, less  $\text{Na}^+$  is in the forming urine, and most will be reabsorbed before reaching the macula densa, which will result in decreased ATP and adenosine, allowing the afferent arteriole to dilate and increase GFR. NO has the opposite effect, relaxing the afferent arteriole at the same time ATP and adenosine are stimulating it to contract. Thus, NO fine-tunes the effects of adenosine and ATP on GFR.

### Paracrine Mechanisms Controlling Glomerular Filtration Rate

Change in GFR	NaCl Absorption	Role of ATP and adenosine/Role of NO	Effect on GFR
Increased GFR	Tubular NaCl increases	ATP and adenosine increase, causing vasoconstriction	Vasoconstriction slows GFR
Decreased GFR	Tubular NaCl decreases	ATP and adenosine decrease, causing vasodilation	Vasodilation increases GFR
Increased GFR	Tubular NaCl increases	NO increases, causing vasodilation	Vasodilation increases GFR
Decreased GFR	Tubular NaCl decreases	NO decreases, causing vasoconstriction	Vasoconstriction decreases GFR

**Table 25.7**

## 25.8 | Endocrine Regulation of Kidney Function

By the end of this section, you will be able to:

- Describe how each of the following functions in the extrinsic control of GFR: renin–angiotensin mechanism, natriuretic peptides, and sympathetic adrenergic activity
- Describe how each of the following works to regulate reabsorption and secretion, so as to affect urine volume and composition: renin–angiotensin system, aldosterone, antidiuretic hormone, and natriuretic peptides
- Name and define the roles of other hormones that regulate kidney control

Several hormones have specific, important roles in regulating kidney function. They act to stimulate or inhibit blood flow.

Some of these are endocrine, acting from a distance, whereas others are paracrine, acting locally.

## Renin–Angiotensin–Aldosterone

Renin is an enzyme that is produced by the granular cells of the afferent arteriole at the JGA. It enzymatically converts angiotensinogen (made by the liver, freely circulating) into angiotensin I. Its release is stimulated by prostaglandins and NO from the JGA in response to decreased extracellular fluid volume.

ACE is not a hormone but it is functionally important in regulating systemic blood pressure and kidney function. It is produced in the lungs but binds to the surfaces of endothelial cells in the afferent arterioles and glomerulus. It enzymatically converts inactive angiotensin I into active angiotensin II. ACE is important in raising blood pressure. People with high blood pressure are sometimes prescribed ACE inhibitors to lower their blood pressure.

Angiotensin II is a potent vasoconstrictor that plays an immediate role in the regulation of blood pressure. It acts systemically to cause vasoconstriction as well as constriction of both the afferent and efferent arterioles of the glomerulus. In instances of blood loss or dehydration, it reduces both GFR and renal blood flow, thereby limiting fluid loss and preserving blood volume. Its release is usually stimulated by decreases in blood pressure, and so the preservation of adequate blood pressure is its primary role.

Aldosterone, often called the “salt-retaining hormone,” is released from the adrenal cortex in response to angiotensin II or directly in response to increased plasma  $K^+$ . It promotes  $Na^+$  reabsorption by the nephron, promoting the retention of water. It is also important in regulating  $K^+$ , promoting its excretion. (This dual effect on two minerals and its origin in the adrenal cortex explains its designation as a mineralocorticoid.) As a result, renin has an immediate effect on blood pressure due to angiotensin II–stimulated vasoconstriction and a prolonged effect through  $Na^+$  recovery due to aldosterone. At the same time that aldosterone causes increased recovery of  $Na^+$ , it also causes greater loss of  $K^+$ . Progesterone is a steroid that is structurally similar to aldosterone. It binds to the aldosterone receptor and weakly stimulates  $Na^+$  reabsorption and increased water recovery. This process is unimportant in men due to low levels of circulating progesterone. It may cause increased retention of water during some periods of the menstrual cycle in women when progesterone levels increase.

## Antidiuretic Hormone (ADH)

Diuretics are drugs that can increase water loss by interfering with the recapture of solutes and water from the forming urine. They are often prescribed to lower blood pressure. Coffee, tea, and alcoholic beverages are familiar diuretics. ADH, a 9-amino acid peptide released by the posterior pituitary, works to do the exact opposite. It promotes the recovery of water, decreases urine volume, and maintains plasma osmolarity and blood pressure. It does so by stimulating the movement of aquaporin proteins into the apical cell membrane of principal cells of the collecting ducts to form water channels, allowing the transcellular movement of water from the lumen of the collecting duct into the interstitial space in the medulla of the kidney by osmosis. From there, it enters the vasa recta capillaries to return to the circulation. Water is attracted by the high osmotic environment of the deep kidney medulla.

## Endothelin

**Endothelins**, 21-amino acid peptides, are extremely powerful vasoconstrictors. They are produced by endothelial cells of the renal blood vessels, mesangial cells, and cells of the DCT. Hormones stimulating endothelin release include angiotensin II, bradykinin, and epinephrine. They do not typically influence blood pressure in healthy people. On the other hand, in people with diabetic kidney disease, endothelin is chronically elevated, resulting in sodium retention. They also diminish GFR by damaging the podocytes and by potently vasoconstricting both the afferent and efferent arterioles.

## Natriuretic Hormones

Natriuretic hormones are peptides that stimulate the kidneys to excrete sodium—an effect opposite that of aldosterone. Natriuretic hormones act by inhibiting aldosterone release and therefore inhibiting  $Na^+$  recovery in the collecting ducts. If  $Na^+$  remains in the forming urine, its osmotic force will cause a concurrent loss of water. Natriuretic hormones also inhibit ADH release, which of course will result in less water recovery. Therefore, natriuretic peptides inhibit both  $Na^+$  and water recovery. One example from this family of hormones is atrial natriuretic hormone (ANH), a 28-amino acid peptide produced by heart atria in response to over-stretching of the atrial wall. The over-stretching occurs in persons with elevated blood pressure or heart failure. It increases GFR through concurrent vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole. These events lead to an increased loss of water and sodium in the forming urine. It also decreases sodium reabsorption in the DCT. There is also B-type natriuretic peptide (BNP) of 32 amino acids produced in the ventricles of the heart. It has a 10-fold lower affinity for its receptor, so its effects are less than those of ANH. Its role may be to provide “fine tuning” for the regulation of blood pressure. BNP’s longer biological half-life makes it a good diagnostic marker

of congestive heart failure (**Figure 25.21**).

## Parathyroid Hormone

Parathyroid hormone (PTH) is an 84-amino acid peptide produced by the parathyroid glands in response to decreased circulating  $\text{Ca}^{++}$  levels. Among its targets is the PCT, where it stimulates the hydroxylation of calcidiol to calcitriol (1,25-hydroxycholecalciferol, the active form of vitamin D). It also blocks reabsorption of phosphate ( $\text{PO}_3^-$ ), causing its loss in the urine. The retention of phosphate would result in the formation of calcium phosphate in the plasma, reducing circulating  $\text{Ca}^{++}$  levels. By ridding the blood of phosphate, higher circulating  $\text{Ca}^{++}$  levels are permitted.

	Stimulus	Effect on GFR	Effect on RBF
<b>VASOCONSTRICTORS</b>			
Sympathetic nerves (epinephrine and norepinephrine)	↓ ECFV	↓	↓
Angiotensin II	↓ ECFV	↓	↓
Endothelin	↑ Stretch, bradykinin, angiotensin II, epinephrine ↓ ECFV	↓	↓
<b>VASODILATORS</b>			
Prostaglandins (PGE1, PGE2, and PGI2)	↓ ECFV ↑ shear stress, angiotensin II	No change/↑	↑
Nitric oxide (NO)	↑ shear stress, acetylcholine, histamine, bradykinin, ATP, adenosine	↑	↑
Bradykinin	Prostaglandins, ↓ ACE	↑	↑
Natriuretic peptides (ANP, B-type)	↑ ECFV	↑	No change
ACE = angiotensin-converting enzyme; ECFV = extracellular fluid volume; GFR = glomerular filtration rate; RBF = renal blood flow; ANP = atrial natriuretic peptide; B-type = ventricular natriuretic peptide			

**Figure 25.21 Major Hormones That Influence GFR and RBF**

## 25.9 | Regulation of Fluid Volume and Composition

By the end of this section, you will be able to:

- Explain the mechanism of action of diuretics
- Explain why the differential permeability or impermeability of specific sections of the nephron tubules is necessary for urine formation

The major hormones influencing total body water are ADH, aldosterone, and ANH. Circumstances that lead to fluid depletion in the body include blood loss and dehydration. Homeostasis requires that volume and osmolarity be preserved. Blood volume is important in maintaining sufficient blood pressure, and there are nonrenal mechanisms involved in its preservation, including vasoconstriction, which can act within seconds of a drop in pressure. Thirst mechanisms are also activated to promote the consumption of water lost through respiration, evaporation, or urination. Hormonal mechanisms are activated to recover volume while maintaining a normal osmotic environment. These mechanisms act principally on the kidney.

### Volume-sensing Mechanisms

The body cannot directly measure blood volume, but blood pressure can be measured. Blood pressure often reflects blood

volume and is measured by baroreceptors in the aorta and carotid sinuses. When blood pressure increases, baroreceptors send more frequent action potentials to the central nervous system, leading to widespread vasodilation. Included in this vasodilation are the afferent arterioles supplying the glomerulus, resulting in increased GFR, and water loss by the kidneys. If pressure decreases, fewer action potentials travel to the central nervous system, resulting in more sympathetic stimulation-producing vasoconstriction, which will result in decreased filtration and GFR, and water loss.

Decreased blood pressure is also sensed by the granular cells in the afferent arteriole of the JGA. In response, the enzyme renin is released. You saw earlier in the chapter that renin activity leads to an almost immediate rise in blood pressure as activated angiotensin II produces vasoconstriction. The rise in pressure is sustained by the aldosterone effects initiated by angiotensin II; this includes an increase in  $\text{Na}^+$  retention and water volume. As an aside, late in the menstrual cycle, progesterone has a modest influence on water retention. Due to its structural similarity to aldosterone, progesterone binds to the aldosterone receptor in the collecting duct of the kidney, causing the same, albeit weaker, effect on  $\text{Na}^+$  and water retention.

Cardiomyocytes of the atria also respond to greater stretch (as blood pressure rises) by secreting ANH. ANH opposes the action of aldosterone by inhibiting the recovery of  $\text{Na}^+$  by the DCT and collecting ducts. More  $\text{Na}^+$  is lost, and as water follows, total blood volume and pressure decline. In low-pressure states, ANH does not seem to have much effect.

ADH is also called vasopressin. Early researchers found that in cases of unusually high secretion of ADH, the hormone caused vasoconstriction (vasopressor activity, hence the name). Only later were its antidiuretic properties identified. Synthetic ADH is still used occasionally to stem life-threatening esophagus bleeding in alcoholics.

When blood volume drops 5–10 percent, causing a decrease in blood pressure, there is a rapid and significant increase in ADH release from the posterior pituitary. Immediate vasoconstriction to increase blood pressure is the result. ADH also causes activation of aquaporin channels in the collecting ducts to affect the recovery of water to help restore vascular volume.

## Diuretics and Fluid Volume

A **diuretic** is a compound that increases urine volume. Three familiar drinks contain diuretic compounds: coffee, tea, and alcohol. The caffeine in coffee and tea works by promoting vasodilation in the nephron, which increases GFR. Alcohol increases GFR by inhibiting ADH release from the posterior pituitary, resulting in less water recovery by the collecting duct. In cases of high blood pressure, diuretics may be prescribed to reduce blood volume and, thereby, reduce blood pressure. The most frequently prescribed anti-hypertensive diuretic is hydrochlorothiazide. It inhibits the  $\text{Na}^+ / \text{Cl}^-$  symporter in the DCT and collecting duct. The result is a loss of  $\text{Na}^+$  with water following passively by osmosis.

Osmotic diuretics promote water loss by osmosis. An example is the indigestible sugar mannitol, which is most often administered to reduce brain swelling after head injury. However, it is not the only sugar that can produce a diuretic effect. In cases of poorly controlled diabetes mellitus, glucose levels exceed the capacity of the tubular glucose symporters, resulting in glucose in the urine. The unrecovered glucose becomes a powerful osmotic diuretic. Classically, in the days before glucose could be detected in the blood and urine, clinicians identified diabetes mellitus by the three Ps: polyuria (diuresis), polydipsia (increased thirst), and polyphagia (increased hunger).

## Regulation of Extracellular $\text{Na}^+$

Sodium has a very strong osmotic effect and attracts water. It plays a larger role in the osmolarity of the plasma than any other circulating component of the blood. If there is too much  $\text{Na}^+$  present, either due to poor control or excess dietary consumption, a series of metabolic problems ensue. There is an increase in total volume of water, which leads to hypertension (high blood pressure). Over a long period, this increases the risk of serious complications such as heart attacks, strokes, and aneurysms. It can also contribute to system-wide edema (swelling).

Mechanisms for regulating  $\text{Na}^+$  concentration include the renin–angiotensin–aldosterone system and ADH (see **Figure 25.14**). Aldosterone stimulates the uptake of  $\text{Na}^+$  on the apical cell membrane of cells in the DCT and collecting ducts, whereas ADH helps to regulate  $\text{Na}^+$  concentration indirectly by regulating the reabsorption of water.

## Regulation of Extracellular $\text{K}^+$

Potassium is present in a 30-fold greater concentration inside the cell than outside the cell. A generalization can be made that  $\text{K}^+$  and  $\text{Na}^+$  concentrations will move in opposite directions. When more  $\text{Na}^+$  is reabsorbed, more  $\text{K}^+$  is secreted; when less  $\text{Na}^+$  is reabsorbed (leading to excretion by the kidney), more  $\text{K}^+$  is retained. When aldosterone causes a recovery of  $\text{Na}^+$  in the nephron, a negative electrical gradient is created that promotes the secretion of  $\text{K}^+$  and  $\text{Cl}^-$  into the lumen.

## Regulation of $\text{Cl}^-$

Chloride is important in acid–base balance in the extracellular space and has other functions, such as in the stomach, where it combines with hydrogen ions in the stomach lumen to form hydrochloric acid, aiding digestion. Its close association with  $\text{Na}^+$  in the extracellular environment makes it the dominant anion of this compartment, and its regulation closely mirrors that of  $\text{Na}^+$ .

## Regulation of $\text{Ca}^{++}$ and Phosphate

The parathyroid glands monitor and respond to circulating levels of  $\text{Ca}^{++}$  in the blood. When levels drop too low, PTH is released to stimulate the DCT to reabsorb  $\text{Ca}^{++}$  from the forming urine. When levels are adequate or high, less PTH is released and more  $\text{Ca}^{++}$  remains in the forming urine to be lost. Phosphate levels move in the opposite direction. When  $\text{Ca}^{++}$  levels are low, PTH inhibits reabsorption of  $\text{HPO}_4^{2-}$  so that its blood level drops, allowing  $\text{Ca}^{++}$  levels to rise. PTH also stimulates the renal conversion of calcidiol into calcitriol, the active form of vitamin D. Calcitriol then stimulates the intestines to absorb more  $\text{Ca}^{++}$  from the diet.

## Regulation of $\text{H}^+$ , Bicarbonate, and pH

The acid–base homeostasis of the body is a function of chemical buffers and physiologic buffering provided by the lungs and kidneys. Buffers, especially proteins,  $\text{HCO}_3^{2-}$ , and ammonia have a very large capacity to absorb or release  $\text{H}^+$  as needed to resist a change in pH. They can act within fractions of a second. The lungs can rid the body of excess acid very rapidly (seconds to minutes) through the conversion of  $\text{HCO}_3^-$  into  $\text{CO}_2$ , which is then exhaled. It is rapid but has limited capacity in the face of a significant acid challenge. The kidneys can rid the body of both acid and base. The renal capacity is large but slow (minutes to hours). The cells of the PCT actively secrete  $\text{H}^+$  into the forming urine as  $\text{Na}^+$  is reabsorbed. The body rids itself of excess  $\text{H}^+$  and raises blood pH. In the collecting ducts, the apical surfaces of intercalated cells have proton pumps that actively secrete  $\text{H}^+$  into the luminal, forming urine to remove it from the body.

As hydrogen ions are pumped into the forming urine, it is buffered by bicarbonate ( $\text{HCO}_3^-$ ),  $\text{H}_2\text{PO}_4^-$  (dihydrogen phosphate ion), or ammonia (forming  $\text{NH}_4^+$ , ammonium ion). Urine pH typically varies in a normal range from 4.5 to 8.0.

## Regulation of Nitrogen Wastes

Nitrogen wastes are produced by the breakdown of proteins during normal metabolism. Proteins are broken down into amino acids, which in turn are deaminated by having their nitrogen groups removed. Deamination converts the amino ( $\text{NH}_2$ ) groups into ammonia ( $\text{NH}_3$ ), ammonium ion ( $\text{NH}_4^+$ ), urea, or uric acid (Figure 25.22). Ammonia is extremely toxic, so most of it is very rapidly converted into urea in the liver. Human urinary wastes typically contain primarily urea with small amounts of ammonium and very little uric acid.

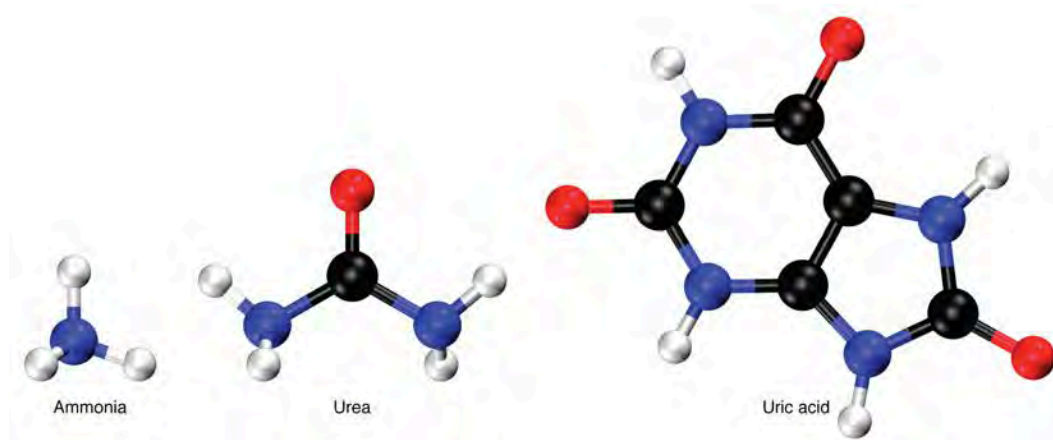


Figure 25.22 Nitrogen Wastes

## Elimination of Drugs and Hormones

Water-soluble drugs may be excreted in the urine and are influenced by one or all of the following processes: glomerular filtration, tubular secretion, or tubular reabsorption. Drugs that are structurally small can be filtered by the glomerulus with the filtrate. Large drug molecules such as heparin or those that are bound to plasma proteins cannot be filtered and are not readily eliminated. Some drugs can be eliminated by carrier proteins that enable secretion of the drug into the tubule lumen. There are specific carriers that eliminate basic (such as dopamine or histamine) or acidic drugs (such as penicillin or indomethacin). As is the case with other substances, drugs may be both filtered and reabsorbed passively along a concentration gradient.

## 25.10 | The Urinary System and Homeostasis

By the end of this section, you will be able to:

- Describe the role of the kidneys in vitamin D activation
- Describe the role of the kidneys in regulating erythropoiesis
- Provide specific examples to demonstrate how the urinary system responds to maintain homeostasis in the body
- Explain how the urinary system relates to other body systems in maintaining homeostasis
- Predict factors or situations affecting the urinary system that could disrupt homeostasis
- Predict the types of problems that would occur in the body if the urinary system could not maintain homeostasis

All systems of the body are interrelated. A change in one system may affect all other systems in the body, with mild to devastating effects. A failure of urinary continence can be embarrassing and inconvenient, but is not life threatening. The loss of other urinary functions may prove fatal. A failure to synthesize vitamin D is one such example.

### Vitamin D Synthesis

In order for vitamin D to become active, it must undergo a hydroxylation reaction in the kidney, that is, an  $-OH$  group must be added to calcidiol to make calcitriol (1,25-dihydroxycholecalciferol). Activated vitamin D is important for absorption of  $Ca^{++}$  in the digestive tract, its reabsorption in the kidney, and the maintenance of normal serum concentrations of  $Ca^{++}$  and phosphate. Calcium is vitally important in bone health, muscle contraction, hormone secretion, and neurotransmitter release. Inadequate  $Ca^{++}$  leads to disorders like osteoporosis and **osteomalacia** in adults and rickets in children. Deficits may also result in problems with cell proliferation, neuromuscular function, blood clotting, and the inflammatory response. Recent research has confirmed that vitamin D receptors are present in most, if not all, cells of the body, reflecting the systemic importance of vitamin D. Many scientists have suggested it be referred to as a hormone rather than a vitamin.

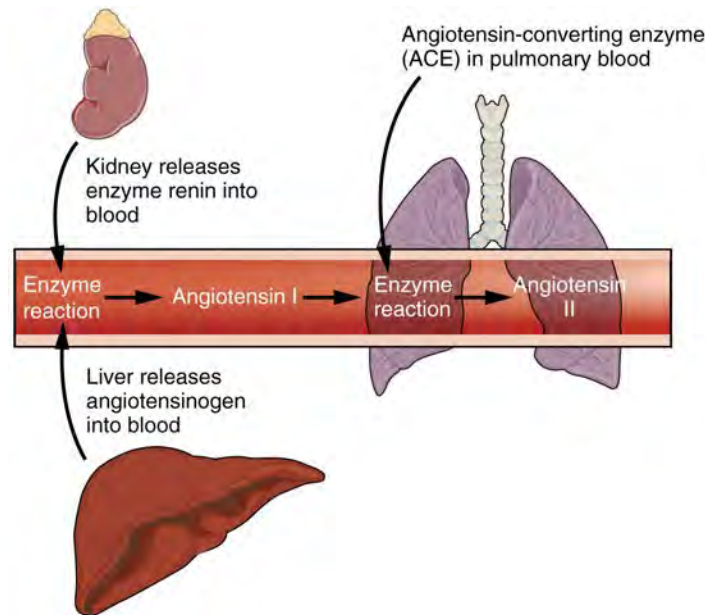
### Erythropoiesis

EPO is a 193-amino acid protein that stimulates the formation of red blood cells in the bone marrow. The kidney produces 85 percent of circulating EPO; the liver, the remainder. If you move to a higher altitude, the partial pressure of oxygen is lower, meaning there is less pressure to push oxygen across the alveolar membrane and into the red blood cell. One way the body compensates is to manufacture more red blood cells by increasing EPO production. If you start an aerobic exercise program, your tissues will need more oxygen to cope, and the kidney will respond with more EPO. If erythrocytes are lost due to severe or prolonged bleeding, or under produced due to disease or severe malnutrition, the kidneys come to the rescue by producing more EPO. Renal failure (loss of EPO production) is associated with anemia, which makes it difficult for the body to cope with increased oxygen demands or to supply oxygen adequately even under normal conditions. Anemia diminishes performance and can be life threatening.

### Blood Pressure Regulation

Due to osmosis, water follows where  $Na^+$  leads. Much of the water the kidneys recover from the forming urine follows the reabsorption of  $Na^+$ . ADH stimulation of aquaporin channels allows for regulation of water recovery in the collecting ducts. Normally, all of the glucose is recovered, but loss of glucose control (diabetes mellitus) may result in an osmotic diuresis severe enough to produce severe dehydration and death. A loss of renal function means a loss of effective vascular volume control, leading to hypotension (low blood pressure) or hypertension (high blood pressure), which can lead to stroke, heart attack, and aneurysm formation.

The kidneys cooperate with the lungs, liver, and adrenal cortex through the renin–angiotensin–aldosterone system (see **Figure 25.14**). The liver synthesizes and secretes the inactive precursor angiotensinogen. When the blood pressure is low, the kidney synthesizes and releases renin. Renin converts angiotensinogen into angiotensin I, and ACE produced in the lung converts angiotensin I into biologically active angiotensin II (**Figure 25.23**). The immediate and short-term effect of angiotensin II is to raise blood pressure by causing widespread vasoconstriction. Angiotensin II also stimulates the adrenal cortex to release the steroid hormone aldosterone, which results in renal reabsorption of  $\text{Na}^+$  and its associated osmotic recovery of water. The reabsorption of  $\text{Na}^+$  helps to raise and maintain blood pressure over a longer term.



**Figure 25.23** The Enzyme Renin Converts the Pro-enzyme Angiotensin

## Regulation of Osmolarity

Blood pressure and osmolarity are regulated in a similar fashion. Severe hypo-osmolarity can cause problems like lysis (rupture) of blood cells or widespread edema, which is due to a solute imbalance. Inadequate solute concentration (such as protein) in the plasma results in water moving toward an area of greater solute concentration, in this case, the interstitial space and cell cytoplasm. If the kidney glomeruli are damaged by an autoimmune illness, large quantities of protein may be lost in the urine. The resultant drop in serum osmolarity leads to widespread edema that, if severe, may lead to damaging or fatal brain swelling. Severe hypertonic conditions may arise with severe dehydration from lack of water intake, severe vomiting, or uncontrolled diarrhea. When the kidney is unable to recover sufficient water from the forming urine, the consequences may be severe (lethargy, confusion, muscle cramps, and finally, death).

## Recovery of Electrolytes

Sodium, calcium, and potassium must be closely regulated. The role of  $\text{Na}^+$  and  $\text{Ca}^{++}$  homeostasis has been discussed at length. Failure of  $\text{K}^+$  regulation can have serious consequences on nerve conduction, skeletal muscle function, and most significantly, on cardiac muscle contraction and rhythm.

## pH Regulation

Recall that enzymes lose their three-dimensional conformation and, therefore, their function if the pH is too acidic or basic. This loss of conformation may be a consequence of the breaking of hydrogen bonds. Move the pH away from the optimum for a specific enzyme and you may severely hamper its function throughout the body, including hormone binding, central nervous system signaling, or myocardial contraction. Proper kidney function is essential for pH homeostasis.

## Everyday CONNECTION

### Stem Cells and Repair of Kidney Damage

Stem cells are unspecialized cells that can reproduce themselves via cell division, sometimes after years of inactivity. Under certain conditions, they may differentiate into tissue-specific or organ-specific cells with special functions. In some cases, stem cells may continually divide to produce a mature cell and to replace themselves. Stem cell therapy has an enormous potential to improve the quality of life or save the lives of people suffering from debilitating or life-threatening diseases. There have been several studies in animals, but since stem cell therapy is still in its infancy, there have been limited experiments in humans.

Acute kidney injury can be caused by a number of factors, including transplants and other surgeries. It affects 7–10 percent of all hospitalized patients, resulting in the deaths of 35–40 percent of inpatients. In limited studies using mesenchymal stem cells, there have been fewer instances of kidney damage after surgery, the length of hospital stays has been reduced, and there have been fewer readmissions after release.

How do these stem cells work to protect or repair the kidney? Scientists are unsure at this point, but some evidence has shown that these stem cells release several growth factors in endocrine and paracrine ways. As further studies are conducted to assess the safety and effectiveness of stem cell therapy, we will move closer to a day when kidney injury is rare, and curative treatments are routine.

## KEY TERMS

**anatomical sphincter** smooth or skeletal muscle surrounding the lumen of a vessel or hollow organ that can restrict flow when contracted

**angiotensin I** protein produced by the enzymatic action of renin on angiotensinogen; inactive precursor of angiotensin II

**angiotensin II** protein produced by the enzymatic action of ACE on inactive angiotensin I; actively causes vasoconstriction and stimulates aldosterone release by the adrenal cortex

**angiotensin-converting enzyme (ACE)** enzyme produced by the lungs that catalyzes the reaction of inactive angiotensin I into active angiotensin II

**angiotensinogen** inactive protein in the circulation produced by the liver; precursor of angiotensin I; must be modified by the enzymes renin and ACE to be activated

**anuria** absence of urine produced; production of 50 mL or less per day

**aquaporin** protein-forming water channels through the lipid bilayer of the cell; allows water to cross; activation in the collecting ducts is under the control of ADH

**Bowman's capsule** cup-shaped sack lined by a simple squamous epithelium (parietal surface) and specialized cells called podocytes (visceral surface) that participate in the filtration process; receives the filtrate which then passes on to the PCTs

**brush border** formed by microvilli on the surface of certain cuboidal cells; in the kidney it is found in the PCT; increases surface area for absorption in the kidney

**calyces** cup-like structures receiving urine from the collecting ducts where it passes on to the renal pelvis and ureter

**cortical nephrons** nephrons with loops of Henle that do not extend into the renal medulla

**countercurrent multiplier system** involves the descending and ascending loops of Henle directing forming urine in opposing directions to create a concentration gradient when combined with variable permeability and sodium pumping

**detrusor muscle** smooth muscle in the bladder wall; fibers run in all directions to reduce the size of the organ when emptying it of urine

**distal convoluted tubules** portions of the nephron distal to the loop of Henle that receive hyposmotic filtrate from the loop of Henle and empty into collecting ducts

**diuretic** compound that increases urine output, leading to decreased water conservation

**efferent arteriole** arteriole carrying blood from the glomerulus to the capillary beds around the convoluted tubules and loop of Henle; portion of the portal system

**endothelins** group of vasoconstrictive, 21-amino acid peptides; produced by endothelial cells of the renal blood vessels, mesangial cells, and cells of the DCT

**external urinary sphincter** skeletal muscle; must be relaxed consciously to void urine

**fenestrations** small windows through a cell, allowing rapid filtration based on size; formed in such a way as to allow substances to cross through a cell without mixing with cell contents

**filtration slits** formed by pedicels of podocytes; substances filter between the pedicels based on size

**forming urine** filtrate undergoing modifications through secretion and reabsorption before true urine is produced

**glomerular filtration rate (GFR)** rate of renal filtration

- glomerulus** tuft of capillaries surrounded by Bowman's capsule; filters the blood based on size
- glycosuria** presence of glucose in the urine; caused by high blood glucose levels that exceed the ability of the kidneys to reabsorb the glucose; usually the result of untreated or poorly controlled diabetes mellitus
- incontinence** loss of ability to control micturition
- intercalated cell** specialized cell of the collecting ducts that secrete or absorb acid or bicarbonate; important in acid–base balance
- internal urinary sphincter** smooth muscle at the juncture of the bladder and urethra; relaxes as the bladder fills to allow urine into the urethra
- inulin** plant polysaccharide injected to determine GFR; is neither secreted nor absorbed by the kidney, so its appearance in the urine is directly proportional to its filtration rate
- juxtaglomerular apparatus (JGA)** located at the juncture of the DCT and the afferent and efferent arterioles of the glomerulus; plays a role in the regulation of renal blood flow and GFR
- juxtaglomerular cell** modified smooth muscle cells of the afferent arteriole; secretes renin in response to a drop in blood pressure
- juxtamedullary nephrons** nephrons adjacent to the border of the cortex and medulla with loops of Henle that extend into the renal medulla
- leaky tight junctions** tight junctions in which the sealing strands of proteins between the membranes of adjacent cells are fewer in number and incomplete; allows limited intercellular movement of solvent and solutes
- leukocyte esterase** enzyme produced by leukocytes that can be detected in the urine and that serves as an indirect indicator of urinary tract infection
- loop of Henle** descending and ascending portions between the proximal and distal convoluted tubules; those of cortical nephrons do not extend into the medulla, whereas those of juxtamedullary nephrons do extend into the medulla
- macula densa** cells found in the part of the DCT forming the JGA; sense  $\text{Na}^+$  concentration in the forming urine
- medulla** inner region of kidney containing the renal pyramids
- mesangial** contractile cells found in the glomerulus; can contract or relax to regulate filtration rate
- micturition** also called urination or voiding
- myogenic mechanism** mechanism by which smooth muscle responds to stretch by contracting; an increase in blood pressure causes vasoconstriction and a decrease in blood pressure causes vasodilation so that blood flow downstream remains steady
- nephrons** functional units of the kidney that carry out all filtration and modification to produce urine; consist of renal corpuscles, proximal and distal convoluted tubules, and descending and ascending loops of Henle; drain into collecting ducts
- net filtration pressure (NFP)** pressure of fluid across the glomerulus; calculated by taking the hydrostatic pressure of the capillary and subtracting the colloid osmotic pressure of the blood and the hydrostatic pressure of Bowman's capsule
- oliguria** below normal urine production of 400–500 mL/day
- osteomalacia** softening of bones due to a lack of mineralization with calcium and phosphate; most often due to lack of vitamin D; in children, osteomalacia is termed rickets; not to be confused with osteoporosis
- pedicels** finger-like projections of podocytes surrounding glomerular capillaries; interdigitate to form a filtration membrane

**peritubular capillaries** second capillary bed of the renal portal system; surround the proximal and distal convoluted tubules; associated with the vasa recta

**physiological sphincter** sphincter consisting of circular smooth muscle indistinguishable from adjacent muscle but possessing differential innervations, permitting its function as a sphincter; structurally weak

**podocytes** cells forming finger-like processes; form the visceral layer of Bowman's capsule; pedicels of the podocytes interdigitate to form a filtration membrane

**polyuria** urine production in excess of 2.5 L/day; may be caused by diabetes insipidus, diabetes mellitus, or excessive use of diuretics

**principal cell** found in collecting ducts and possess channels for the recovery or loss of sodium and potassium; under the control of aldosterone; also have aquaporin channels under ADH control to regulate recovery of water

**proximal convoluted tubules (PCTs)** tortuous tubules receiving filtrate from Bowman's capsule; most active part of the nephron in reabsorption and secretion

**renal columns** extensions of the renal cortex into the renal medulla; separates the renal pyramids; contains blood vessels and connective tissues

**renal corpuscle** consists of the glomerulus and Bowman's capsule

**renal cortex** outer part of kidney containing all of the nephrons; some nephrons have loops of Henle extending into the medulla

**renal fat pad** adipose tissue between the renal fascia and the renal capsule that provides protective cushioning to the kidney

**renal hilum** recessed medial area of the kidney through which the renal artery, renal vein, ureters, lymphatics, and nerves pass

**renal papillae** medullary area of the renal pyramids where collecting ducts empty urine into the minor calyces

**renal pyramids** six to eight cone-shaped tissues in the medulla of the kidney containing collecting ducts and the loops of Henle of juxtamedullary nephrons

**renin** enzyme produced by juxtaglomerular cells in response to decreased blood pressure or sympathetic nervous activity; catalyzes the conversion of angiotensinogen into angiotensin I

**retroperitoneal** outside the peritoneal cavity; in the case of the kidney and ureters, between the parietal peritoneum and the abdominal wall

**sacral micturition center** group of neurons in the sacral region of the spinal cord that controls urination; acts reflexively unless its action is modified by higher brain centers to allow voluntary urination

**specific gravity** weight of a liquid compared to pure water, which has a specific gravity of 1.0; any solute added to water will increase its specific gravity

**systemic edema** increased fluid retention in the interstitial spaces and cells of the body; can be seen as swelling over large areas of the body, particularly the lower extremities

**trigone** area at the base of the bladder marked by the two ureters in the posterior-lateral aspect and the urethral orifice in the anterior aspect oriented like points on a triangle

**tubuloglomerular feedback** feedback mechanism involving the JGA; macula densa cells monitor  $\text{Na}^+$  concentration in the terminal portion of the ascending loop of Henle and act to cause vasoconstriction or vasodilation of afferent and efferent arterioles to alter GFR

**urethra** transports urine from the bladder to the outside environment

**urinalysis** analysis of urine to diagnose disease

**urochrome** heme-derived pigment that imparts the typical yellow color of urine

**vasa recta** branches of the efferent arterioles that parallel the course of the loops of Henle and are continuous with the peritubular capillaries; with the glomerulus, form a portal system

## CHAPTER REVIEW

### 25.1 Physical Characteristics of Urine

The kidney glomerulus filters blood mainly based on particle size to produce a filtrate lacking cells or large proteins. Most of the ions and molecules in the filtrate are needed by the body and must be reabsorbed farther down the nephron tubules, resulting in the formation of urine. Urine characteristics change depending on water intake, exercise, environmental temperature, and nutrient intake. Urinalysis analyzes characteristics of the urine and is used to diagnose diseases. A minimum of 400 to 500 mL urine must be produced daily to rid the body of wastes. Excessive quantities of urine may indicate diabetes insipidus or diabetes mellitus. The pH range of urine is 4.5 to 8.0, and is affected by diet. Osmolarity ranges from 50 to 1200 milliosmoles, and is a reflection of the amount of water being recovered or lost by renal nephrons.

### 25.2 Gross Anatomy of Urine Transport

The urethra is the only urinary structure that differs significantly between males and females. This is due to the dual role of the male urethra in transporting both urine and semen. The urethra arises from the trigone area at the base of the bladder. Urination is controlled by an involuntary internal sphincter of smooth muscle and a voluntary external sphincter of skeletal muscle. The shorter female urethra contributes to the higher incidence of bladder infections in females. The male urethra receives secretions from the prostate gland, Cowper's gland, and seminal vesicles as well as sperm. The bladder is largely retroperitoneal and can hold up to 500–600 mL urine. Micturition is the process of voiding the urine and involves both involuntary and voluntary actions. Voluntary control of micturition requires a mature and intact sacral micturition center. It also requires an intact spinal cord. Loss of control of micturition is called incontinence and results in voiding when the bladder contains about 250 mL urine. The ureters are retroperitoneal and lead from the renal pelvis of the kidney to the trigone area at the base of the bladder. A thick muscular wall consisting of longitudinal and circular smooth muscle helps move urine toward the bladder by way of peristaltic contractions.

### 25.3 Gross Anatomy of the Kidney

As noted previously, the structure of the kidney is divided into two principle regions—the peripheral rim of cortex and the central medulla. The two kidneys receive about 25 percent of cardiac output. They are protected in the retroperitoneal space by the renal fat pad and overlying ribs and muscle. Ureters, blood vessels, lymph vessels, and nerves enter and leave at the renal hilum. The renal arteries arise directly from the aorta, and the renal veins drain directly into the inferior vena cava. Kidney function is derived from the actions of about 1.3 million nephrons per kidney; these are the “functional units.” A capillary bed, the glomerulus, filters blood and the filtrate is captured by Bowman's capsule. A portal system is formed when the blood flows through a second capillary bed surrounding the proximal and distal convoluted tubules and the loop of Henle. Most water and solutes are recovered by this second capillary bed. This filtrate is processed and finally gathered by collecting ducts that drain into the minor calyces, which merge to form major calyces; the filtrate then proceeds to the renal pelvis and finally the ureters.

### 25.4 Microscopic Anatomy of the Kidney

The functional unit of the kidney, the nephron, consists of the renal corpuscle, PCT, loop of Henle, and DCT. Cortical nephrons have short loops of Henle, whereas juxtamedullary nephrons have long loops of Henle extending into the medulla. About 15 percent of nephrons are juxtamedullary. The glomerulus is a capillary bed that filters blood principally based on particle size. The filtrate is captured by Bowman's capsule and directed to the PCT. A filtration membrane is formed by the fused basement membranes of the podocytes and the capillary endothelial cells that they embrace. Contractile mesangial cells further perform a role in regulating the rate at which the blood is filtered. Specialized cells in the JGA produce paracrine signals to regulate blood flow and filtration rates of the glomerulus. Other JGA cells produce the enzyme renin, which plays a central role in blood pressure regulation. The filtrate enters the PCT where absorption and secretion of several substances occur. The descending and ascending limbs of the loop of Henle consist of thick and thin segments. Absorption and secretion continue in the DCT but to a lesser extent than in the PCT. Each collecting duct collects forming urine from several nephrons and responds to the posterior pituitary hormone ADH by inserting aquaporin water channels into the cell membrane to fine tune water recovery.

## 25.5 Physiology of Urine Formation

The entire volume of the blood is filtered through the kidneys about 300 times per day, and 99 percent of the water filtered is recovered. The GFR is influenced by hydrostatic pressure and colloid osmotic pressure. Under normal circumstances, hydrostatic pressure is significantly greater and filtration occurs. The hydrostatic pressure of the glomerulus depends on systemic blood pressure, autoregulatory mechanisms, sympathetic nervous activity, and paracrine hormones. The kidney can function normally under a wide range of blood pressures due to the autoregulatory nature of smooth muscle.

## 25.6 Tubular Reabsorption

The kidney regulates water recovery and blood pressure by producing the enzyme renin. It is renin that starts a series of reactions, leading to the production of the vasoconstrictor angiotensin II and the salt-retaining steroid aldosterone. Water recovery is also powerfully and directly influenced by the hormone ADH. Even so, it only influences the last 10 percent of water available for recovery after filtration at the glomerulus, because 90 percent of water is recovered before reaching the collecting ducts. Depending on the body's fluid status at any given time, the collecting ducts can recover none or almost all of the water reaching them.

Mechanisms of solute recovery include active transport, simple diffusion, and facilitated diffusion. Most filtered substances are reabsorbed. Urea,  $\text{NH}_3$ , creatinine, and some drugs are filtered or secreted as wastes.  $\text{H}^+$  and  $\text{HCO}_3^-$  are secreted or reabsorbed as needed to maintain acid–base balance. Movement of water from the glomerulus is primarily due to pressure, whereas that of peritubular capillaries and vasa recta is due to osmolarity and concentration gradients. The PCT is the most metabolically active part of the nephron and uses a wide array of protein micromachines to maintain homeostasis—symporters, antiporters, and ATPase active transporters—in conjunction with diffusion, both simple and facilitated. Almost 100 percent of glucose, amino acids, and vitamins are recovered in the PCT. Bicarbonate ( $\text{HCO}_3^-$ ) is recovered using the same enzyme, carbonic anhydrase (CA), found in erythrocytes. The recovery of solutes creates an osmotic gradient to promote the recovery of water. The descending loop of the juxtglomerular nephrons reaches an osmolarity of up to 1200 mOsmol/kg, promoting the recovery of water. The ascending loop is impervious to water but actively recovers  $\text{Na}^+$ , reducing filtrate osmolarity to 50–100 mOsmol/kg. The descending and ascending loop and vasa recta form a countercurrent multiplier system to increase  $\text{Na}^+$  concentration in the kidney medulla. The collecting ducts actively pump urea into the medulla, further contributing to the high osmotic environment. The vasa recta recover the solute and water in the medulla, returning them to the circulation. Nearly 90 percent of water is recovered before the forming urine reaches the DCT, which will recover another 10 percent. Calcium recovery in the DCT is influenced by PTH and active vitamin D. In the collecting ducts, ADH stimulates aquaporin channel insertion to increase water recovery and thereby regulate osmolarity of the blood. Aldosterone stimulates  $\text{Na}^+$  recovery by the collecting duct.

## 25.7 Regulation of Renal Blood Flow

The kidneys are innervated by sympathetic nerves of the autonomic nervous system. Sympathetic nervous activity decreases blood flow to the kidney, making more blood available to other areas of the body during times of stress. The arteriolar myogenic mechanism maintains a steady blood flow by causing arteriolar smooth muscle to contract when blood pressure increases and causing it to relax when blood pressure decreases. Tubuloglomerular feedback involves paracrine signaling at the JGA to cause vasoconstriction or vasodilation to maintain a steady rate of blood flow.

## 25.8 Endocrine Regulation of Kidney Function

Endocrine hormones act from a distance and paracrine hormones act locally. The renal enzyme renin converts angiotensinogen into angiotensin I. The lung enzyme, ACE, converts angiotensin I into active angiotensin II. Angiotensin II is an active vasoconstrictor that increases blood pressure. Angiotensin II also stimulates aldosterone release from the adrenal cortex, causing the collecting duct to retain  $\text{Na}^+$ , which promotes water retention and a longer-term rise in blood pressure. ADH promotes water recovery by the collecting ducts by stimulating the insertion of aquaporin water channels into cell membranes. Endothelins are elevated in cases of diabetic kidney disease, increasing  $\text{Na}^+$  retention and decreasing GFR. Natriuretic hormones, released primarily from the atria of the heart in response to stretching of the atrial walls, stimulate  $\text{Na}^+$  excretion and thereby decrease blood pressure. PTH stimulates the final step in the formation of active vitamin D3 and reduces phosphate reabsorption, resulting in higher circulating  $\text{Ca}^{++}$  levels.

## 25.9 Regulation of Fluid Volume and Composition

The major hormones regulating body fluids are ADH, aldosterone and ANH. Progesterone is similar in structure to

aldosterone and can bind to and weakly stimulate aldosterone receptors, providing a similar but diminished response. Blood pressure is a reflection of blood volume and is monitored by baroreceptors in the aortic arch and carotid sinuses. When blood pressure increases, more action potentials are sent to the central nervous system, resulting in greater vasodilation, greater GFR, and more water lost in the urine. ANH is released by the cardiomyocytes when blood pressure increases, causing  $\text{Na}^+$  and water loss. ADH at high levels causes vasoconstriction in addition to its action on the collecting ducts to recover more water. Diuretics increase urine volume. Mechanisms for controlling  $\text{Na}^+$  concentration in the blood include the renin–angiotensin–aldosterone system and ADH. When  $\text{Na}^+$  is retained,  $\text{K}^+$  is excreted; when  $\text{Na}^+$  is lost,  $\text{K}^+$  is retained. When circulating  $\text{Ca}^{++}$  decreases, PTH stimulates the reabsorption of  $\text{Ca}^{++}$  and inhibits reabsorption of  $\text{HPO}_4^{2-}$ . pH is regulated through buffers, expiration of  $\text{CO}_2$ , and excretion of acid or base by the kidneys. The breakdown of amino acids produces ammonia. Most ammonia is converted into less-toxic urea in the liver and excreted in the urine. Regulation of drugs is by glomerular filtration, tubular secretion, and tubular reabsorption.

## 25.10 The Urinary System and Homeostasis

The effects of failure of parts of the urinary system may range from inconvenient (incontinence) to fatal (loss of filtration and many others). The kidneys catalyze the final reaction in the synthesis of active vitamin D that in turn helps regulate  $\text{Ca}^{++}$ . The kidney hormone EPO stimulates erythrocyte development and promotes adequate  $\text{O}_2$  transport. The kidneys help regulate blood pressure through  $\text{Na}^+$  and water retention and loss. The kidneys work with the adrenal cortex, lungs, and liver in the renin–angiotensin–aldosterone system to regulate blood pressure. They regulate osmolarity of the blood by regulating both solutes and water. Three electrolytes are more closely regulated than others:  $\text{Na}^+$ ,  $\text{Ca}^{++}$ , and  $\text{K}^+$ . The kidneys share pH regulation with the lungs and plasma buffers, so that proteins can preserve their three-dimensional conformation and thus their function.

## REVIEW QUESTIONS

- Diabetes insipidus or diabetes mellitus would most likely be indicated by \_\_\_\_\_.
  - anuria
  - polyuria
  - oliguria
  - none of the above
- The color of urine is determined mainly by \_\_\_\_\_.
  - diet
  - filtration rate
  - byproducts of red blood cell breakdown
  - filtration efficiency
- Production of less than 50 mL/day of urine is called \_\_\_\_\_.
  - normal
  - polyuria
  - oliguria
  - anuria
- Peristaltic contractions occur in the \_\_\_\_\_.
  - urethra
  - bladder
  - ureters
  - urethra, bladder, and ureters
- Somatic motor neurons must be \_\_\_\_\_ to relax the external urethral sphincter to allow urination.
  - stimulated
  - inhibited
- Which part of the urinary system is *not* completely retroperitoneal?
  - kidneys
  - ureters
  - bladder
  - nephrons
- The renal pyramids are separated from each other by extensions of the renal cortex called \_\_\_\_\_.
  - renal medulla
  - minor calyces
  - medullary cortices
  - renal columns
- The primary structure found within the medulla is the \_\_\_\_\_.
  - loop of Henle
  - minor calyces
  - portal system
  - ureter
- The right kidney is slightly lower because \_\_\_\_\_.
  - it is displaced by the liver
  - it is displaced by the heart
  - it is slightly smaller
  - it needs protection of the lower ribs
- Blood filtrate is captured in the lumen of the \_\_\_\_\_.
  - glomerulus
  - Bowman's capsule
  - calyces
  - renal papillae

- 11.** What are the names of the capillaries following the efferent arteriole?
- arcuate and medullary
  - interlobar and interlobular
  - peritubular and vasa recta
  - peritubular and medullary
- 12.** The functional unit of the kidney is called \_\_\_\_\_.
- the renal hilus
  - the renal corpuscle
  - the nephron
  - Bowman's capsule
- 13.** \_\_\_\_\_ pressure must be greater on the capillary side of the filtration membrane to achieve filtration.
- Osmotic
  - Hydrostatic
- 14.** Production of urine to modify plasma makeup is the result of \_\_\_\_\_.
- filtration
  - absorption
  - secretion
  - filtration, absorption, and secretion
- 15.** Systemic blood pressure must stay above 60 so that the proper amount of filtration occurs.
- true
  - false
- 16.** Aquaporin channels are only found in the collecting duct.
- true
  - false
- 17.** Most absorption and secretion occurs in this part of the nephron.
- proximal convoluted tubule
  - descending loop of Henle
  - ascending loop of Henle
  - distal convoluted tubule
  - collecting ducts
- 18.** The fine tuning of water recovery or disposal occurs in \_\_\_\_\_.
- the proximal convoluted tubule
  - the collecting ducts
  - the ascending loop of Henle
  - the distal convoluted tubule
- 19.** Vasodilation of blood vessels to the kidneys is due to \_\_\_\_\_.
- more frequent action potentials
  - less frequent action potentials
- 20.** When blood pressure increases, blood vessels supplying the kidney will \_\_\_\_\_ to mount a steady rate of filtration.
- contract
  - relax
- 21.** Which of these three paracrine chemicals cause vasodilation?
- ATP
  - adenosine
  - nitric oxide
- 22.** What hormone directly opposes the actions of natriuretic hormones?
- renin
  - nitric oxide
  - dopamine
  - aldosterone
- 23.** Which of these is a vasoconstrictor?
- nitric oxide
  - natriuretic hormone
  - bradykinin
  - angiotensin II
- 24.** What signal causes the heart to secrete atrial natriuretic hormone?
- increased blood pressure
  - decreased blood pressure
  - increased  $\text{Na}^+$  levels
  - decreased  $\text{Na}^+$  levels
- 25.** Which of these beverages does *not* have a diuretic effect?
- tea
  - coffee
  - alcohol
  - milk
- 26.** Progesterone can bind to receptors for which hormone that, when released, activates water retention?
- aldosterone
  - ADH
  - PTH
  - ANH
- 27.** Renin is released in response to \_\_\_\_\_.
- increased blood pressure
  - decreased blood pressure
  - ACE
  - diuretics
- 28.** Which step in vitamin D production does the kidney perform?
- converts cholecalciferol into calcidiol
  - converts calcidiol into calcitriol
  - stores vitamin D
  - none of these
- 29.** Which hormone does the kidney produce that stimulates red blood cell production?
- thrombopoietin
  - vitamin D
  - EPO
  - renin

30. If there were no aquaporin channels in the collecting duct, \_\_\_\_\_.
- you would develop systemic edema
  - you would retain excess  $\text{Na}^+$
  - you would lose vitamins and electrolytes
  - you would suffer severe dehydration

## CRITICAL THINKING QUESTIONS

- What is suggested by the presence of white blood cells found in the urine?
- Both diabetes mellitus and diabetes insipidus produce large urine volumes, but how would other characteristics of the urine differ between the two diseases?
- Why are females more likely to contract bladder infections than males?
- Describe how forceful urination is accomplished.
- What anatomical structures provide protection to the kidney?
- How does the renal portal system differ from the hypothalamo–hypophyseal and digestive portal systems?
- Name the structures found in the renal hilum.
- Which structures make up the renal corpuscle?
- What are the major structures comprising the filtration membrane?
- Give the formula for net filtration pressure.
- Name at least five symptoms of kidney failure.
- Which vessels and what part of the nephron are involved in countercurrent multiplication?
- Give the approximate osmolarity of fluid in the proximal convoluted tubule, deepest part of the loop of Henle, distal convoluted tubule, and the collecting ducts.
- Explain what happens to  $\text{Na}^+$  concentration in the nephron when GFR increases.
- If you want the kidney to excrete more  $\text{Na}^+$  in the urine, what do you want the blood flow to do?
- What organs produce which hormones or enzymes in the renin–angiotensin system?
- PTH affects absorption and reabsorption of what?
- Why is ADH also called vasopressin?
- How can glucose be a diuretic?
- How does lack of protein in the blood cause edema?
- Which three electrolytes are most closely regulated by the kidney?

# 26 | FLUID, ELECTROLYTE, AND ACID-BASE BALANCE



**Figure 26.1 Venus Williams Perspiring on the Tennis Court** The body has critically important mechanisms for balancing the intake and output of bodily fluids. An athlete must continuously replace the water and electrolytes lost in sweat. (credit: "Edwin Martinez1"/Wikimedia Commons)

## Introduction

### Chapter Objectives

After studying this chapter, you will be able to:

- Identify the body's main fluid compartments
- Define plasma osmolality and identify two ways in which plasma osmolality is maintained
- Identify the six ions most important to the function of the body
- Define buffer and discuss the role of buffers in the body
- Explain why bicarbonate must be conserved rather than reabsorbed in the kidney
- Identify the normal range of blood pH and name the conditions where one has a blood pH that is either too high or too low

Homeostasis, or the maintenance of constant conditions in the body, is a fundamental property of all living things. In the human body, the substances that participate in chemical reactions must remain within narrow ranges of concentration. Too much or too little of a single substance can disrupt your bodily functions. Because metabolism relies on reactions that are all interconnected, any disruption might affect multiple organs or even organ systems. Water is the most ubiquitous substance in the chemical reactions of life. The interactions of various aqueous solutions—solutions in which water is the solvent—are continuously monitored and adjusted by a large suite of interconnected feedback systems in your body. Understanding the ways in which the body maintains these critical balances is key to understanding good health.

## 26.1 | Body Fluids and Fluid Compartments

By the end of this section, you will be able to:

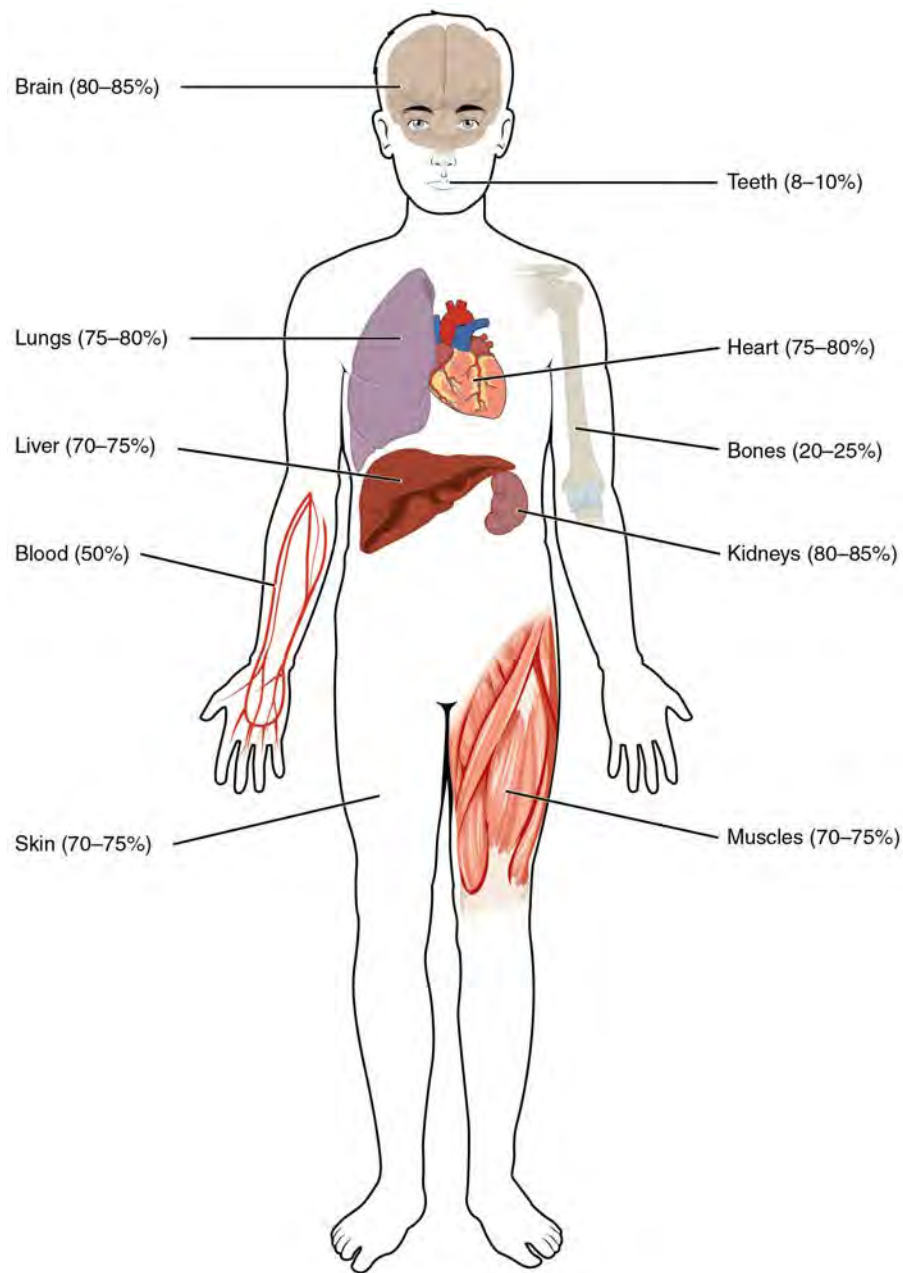
- Explain the importance of water in the body
- Contrast the composition of the intracellular fluid with that of the extracellular fluid
- Explain the importance of protein channels in the movement of solutes
- Identify the causes and symptoms of edema

The chemical reactions of life take place in aqueous solutions. The dissolved substances in a solution are called solutes. In the human body, solutes vary in different parts of the body, but may include proteins—including those that transport lipids, carbohydrates, and, very importantly, electrolytes. Often in medicine, a mineral dissociated from a salt that carries an electrical charge (an ion) is called an electrolyte. For instance, sodium ions ( $\text{Na}^+$ ) and chloride ions ( $\text{Cl}^-$ ) are often referred to as electrolytes.

In the body, water moves through semi-permeable membranes of cells and from one compartment of the body to another by a process called osmosis. Osmosis is basically the diffusion of water from regions of higher concentration to regions of lower concentration, along an osmotic gradient across a semi-permeable membrane. As a result, water will move into and out of cells and tissues, depending on the relative concentrations of the water and solutes found there. An appropriate balance of solutes inside and outside of cells must be maintained to ensure normal function.

### Body Water Content

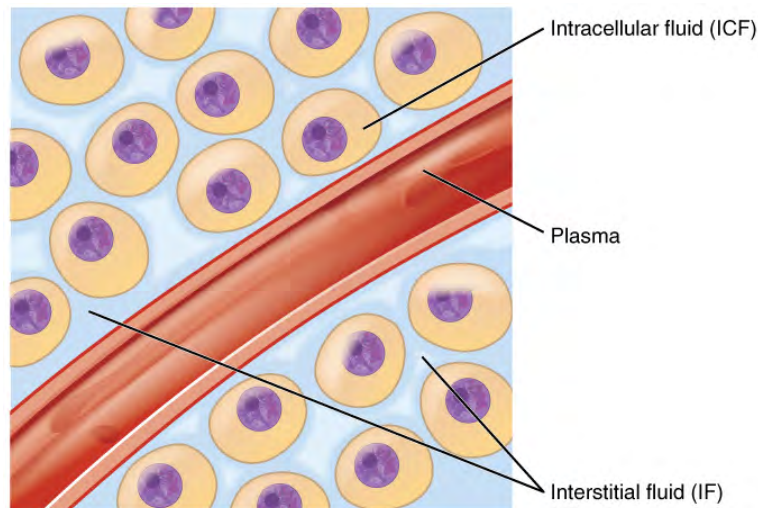
Human beings are mostly water, ranging from about 75 percent of body mass in infants to about 50–60 percent in adult men and women, to as low as 45 percent in old age. The percent of body water changes with development, because the proportions of the body given over to each organ and to muscles, fat, bone, and other tissues change from infancy to adulthood (**Figure 26.2**). Your brain and kidneys have the highest proportions of water, which composes 80–85 percent of their masses. In contrast, teeth have the lowest proportion of water, at 8–10 percent.



**Figure 26.2 Water Content of the Body's Organs and Tissues** Water content varies in different body organs and tissues, from as little as 8 percent in the teeth to as much as 85 percent in the brain.

## Fluid Compartments

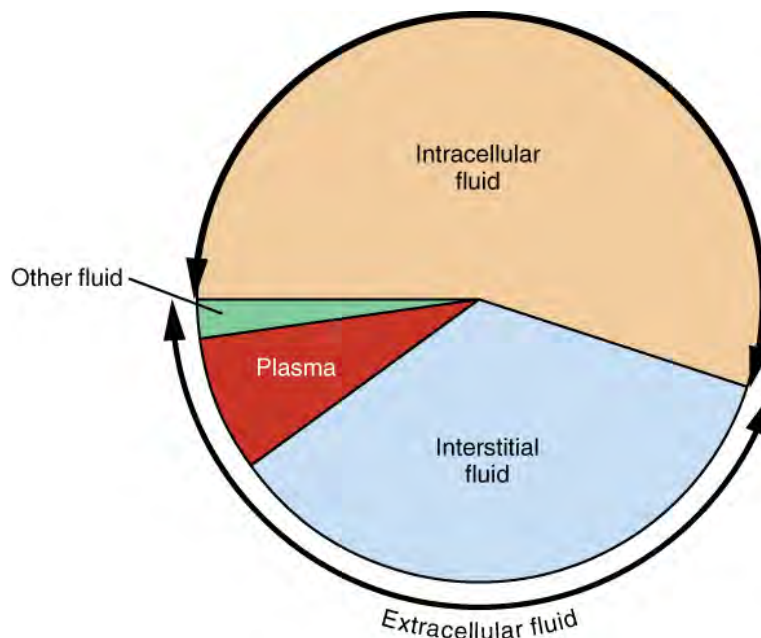
Body fluids can be discussed in terms of their specific **fluid compartment**, a location that is largely separate from another compartment by some form of a physical barrier. The **intracellular fluid (ICF)** compartment is the system that includes all fluid enclosed in cells by their plasma membranes. **Extracellular fluid (ECF)** surrounds all cells in the body. Extracellular fluid has two primary constituents: the fluid component of the blood (called plasma) and the **interstitial fluid (IF)** that surrounds all cells not in the blood (**Figure 26.3**).



**Figure 26.3 Fluid Compartments in the Human Body** The intracellular fluid (ICF) is the fluid within cells. The interstitial fluid (IF) is part of the extracellular fluid (ECF) between the cells. Blood plasma is the second part of the ECF. Materials travel between cells and the plasma in capillaries through the IF.

### Intracellular Fluid

The ICF lies within cells and is the principal component of the cytosol/cytoplasm. The ICF makes up about 60 percent of the total water in the human body, and in an average-size adult male, the ICF accounts for about 25 liters (seven gallons) of fluid (**Figure 26.4**). This fluid volume tends to be very stable, because the amount of water in living cells is closely regulated. If the amount of water inside a cell falls to a value that is too low, the cytosol becomes too concentrated with solutes to carry on normal cellular activities; if too much water enters a cell, the cell may burst and be destroyed.



**Figure 26.4 A Pie Graph Showing the Proportion of Total Body Fluid in Each of the Body's Fluid Compartments** Most of the water in the body is intracellular fluid. The second largest volume is the interstitial fluid, which surrounds cells that are not blood cells.

### Extracellular Fluid

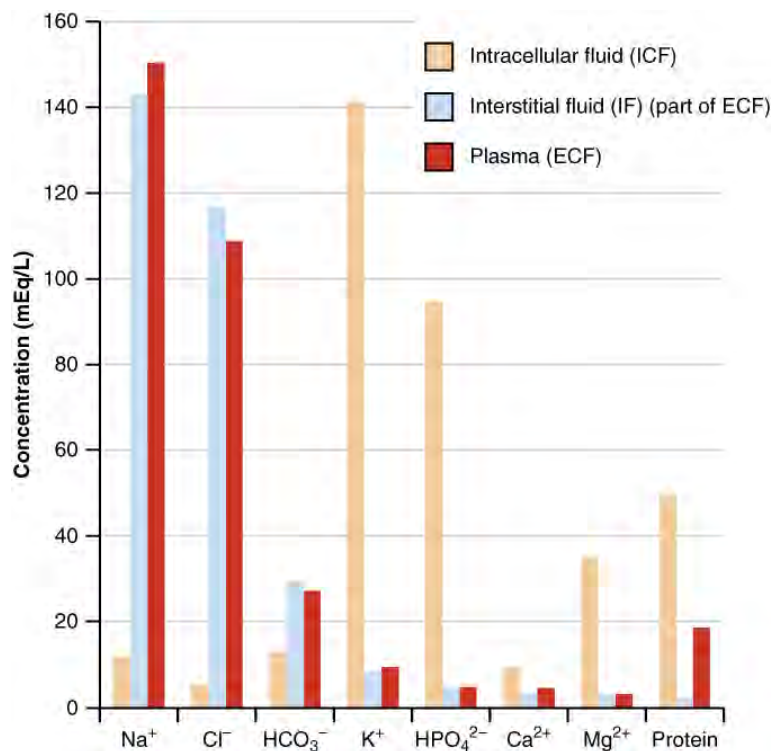
The ECF accounts for the other one-third of the body's water content. Approximately 20 percent of the ECF is found in

plasma. Plasma travels through the body in blood vessels and transports a range of materials, including blood cells, proteins (including clotting factors and antibodies), electrolytes, nutrients, gases, and wastes. Gases, nutrients, and waste materials travel between capillaries and cells through the IF. Cells are separated from the IF by a selectively permeable cell membrane that helps regulate the passage of materials between the IF and the interior of the cell.

The body has other water-based ECF. These include the cerebrospinal fluid that bathes the brain and spinal cord, lymph, the synovial fluid in joints, the pleural fluid in the pleural cavities, the pericardial fluid in the cardiac sac, the peritoneal fluid in the peritoneal cavity, and the aqueous humor of the eye. Because these fluids are outside of cells, these fluids are also considered components of the ECF compartment.

## Composition of Body Fluids

The compositions of the two components of the ECF—plasma and IF—are more similar to each other than either is to the ICF (Figure 26.5). Blood plasma has high concentrations of sodium, chloride, bicarbonate, and protein. The IF has high concentrations of sodium, chloride, and bicarbonate, but a relatively lower concentration of protein. In contrast, the ICF has elevated amounts of potassium, phosphate, magnesium, and protein. Overall, the ICF contains high concentrations of potassium and phosphate ( $\text{HPO}_4^{2-}$ ), whereas both plasma and the ECF contain high concentrations of sodium and chloride.



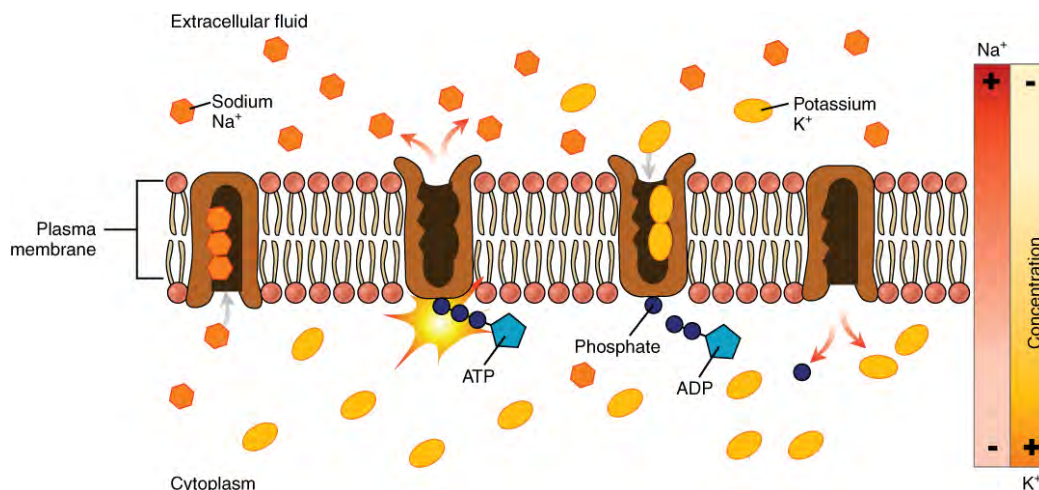
**Figure 26.5 The Concentrations of Different Elements in Key Bodily Fluids** The graph shows the composition of the ICF, IF, and plasma. The compositions of plasma and IF are similar to one another but are quite different from the composition of the ICF.

## Interactive LINK



Watch this [video \(http://openstaxcollege.org/l/bodyfluids\)](http://openstaxcollege.org/l/bodyfluids) to learn more about body fluids, fluid compartments, and electrolytes. When blood volume decreases due to sweating, from what source is water taken in by the blood?

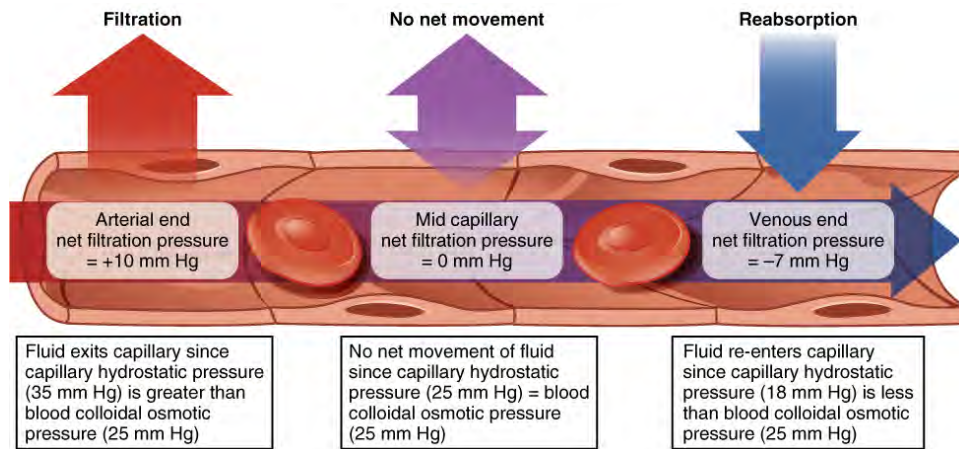
Most body fluids are neutral in charge. Thus, cations, or positively charged ions, and anions, or negatively charged ions, are balanced in fluids. As seen in the previous graph, sodium ( $\text{Na}^+$ ) ions and chloride ( $\text{Cl}^-$ ) ions are concentrated in the ECF of the body, whereas potassium ( $\text{K}^+$ ) ions are concentrated inside cells. Although sodium and potassium can “leak” through “pores” into and out of cells, respectively, the high levels of potassium and low levels of sodium in the ICF are maintained by sodium-potassium pumps in the cell membranes. These pumps use the energy supplied by ATP to pump sodium out of the cell and potassium into the cell (Figure 26.6).



**Figure 26.6 The Sodium-Potassium Pump** The sodium-potassium pump is powered by ATP to transfer sodium out of the cytoplasm and into the ECF. The pump also transfers potassium out of the ECF and into the cytoplasm. (credit: modification of work by Mariana Ruiz Villarreal)

## Fluid Movement between Compartments

**Hydrostatic pressure**, the force exerted by a fluid against a wall, causes movement of fluid between compartments. The hydrostatic pressure of blood is the pressure exerted by blood against the walls of the blood vessels by the pumping action of the heart. In capillaries, hydrostatic pressure (also known as capillary blood pressure) is higher than the opposing “colloid osmotic pressure” in blood—a “constant” pressure primarily produced by circulating albumin—at the arteriolar end of the capillary (Figure 26.7). This pressure forces plasma and nutrients out of the capillaries and into surrounding tissues. Fluid and the cellular wastes in the tissues enter the capillaries at the venule end, where the hydrostatic pressure is less than the osmotic pressure in the vessel. Filtration pressure squeezes fluid from the plasma in the blood to the IF surrounding the tissue cells. The surplus fluid in the interstitial space that is not returned directly back to the capillaries is drained from tissues by the lymphatic system, and then re-enters the vascular system at the subclavian veins.



**Figure 26.7 Capillary Exchange** Net filtration occurs near the arterial end of the capillary since capillary hydrostatic pressure (CHP) is greater than blood colloidal osmotic pressure (BCOP). There is no net movement of fluid near the midpoint of the capillary since  $CHP = BCOP$ . Net reabsorption occurs near the venous end of the capillary since BCOP is greater than CHP.

## Interactive LINK



Watch this [video \(http://openstaxcollege.org/l/dynamicfluid\)](http://openstaxcollege.org/l/dynamicfluid) to see an explanation of the dynamics of fluid in the body's compartments. What happens in the tissue when capillary blood pressure is less than osmotic pressure?

Hydrostatic pressure is especially important in governing the movement of water in the nephrons of the kidneys to ensure proper filtering of the blood to form urine. As hydrostatic pressure in the kidneys increases, the amount of water leaving the capillaries also increases, and more urine filtrate is formed. If hydrostatic pressure in the kidneys drops too low, as can happen in dehydration, the functions of the kidneys will be impaired, and less nitrogenous wastes will be removed from the bloodstream. Extreme dehydration can result in kidney failure.

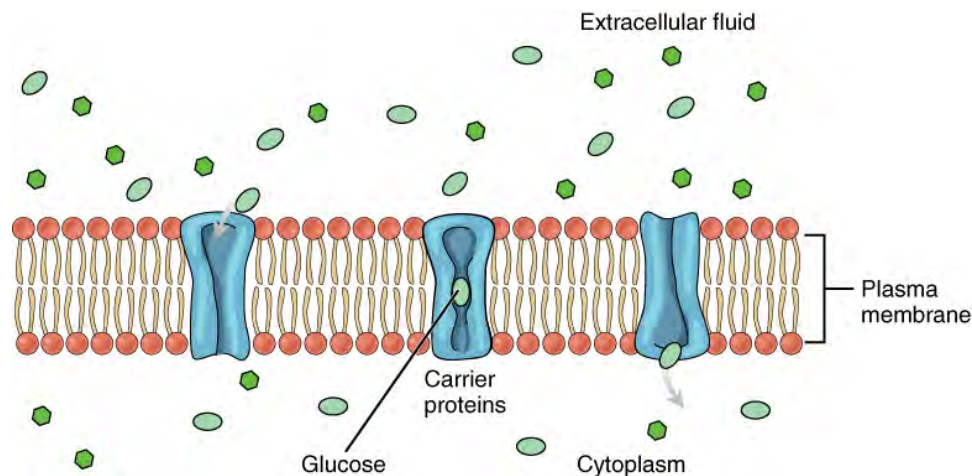
Fluid also moves between compartments along an osmotic gradient. Recall that an osmotic gradient is produced by the difference in concentration of all solutes on either side of a semi-permeable membrane. The magnitude of the osmotic gradient is proportional to the difference in the concentration of solutes on one side of the cell membrane to that on the other side. Water will move by osmosis from the side where its concentration is high (and the concentration of solute is low) to the side of the membrane where its concentration is low (and the concentration of solute is high). In the body, water moves by osmosis from plasma to the IF (and the reverse) and from the IF to the ICF (and the reverse). In the body, water moves constantly into and out of fluid compartments as conditions change in different parts of the body.

For example, if you are sweating, you will lose water through your skin. Sweating depletes your tissues of water and increases the solute concentration in those tissues. As this happens, water diffuses from your blood into sweat glands and surrounding skin tissues that have become dehydrated because of the osmotic gradient. Additionally, as water leaves the blood, it is replaced by the water in other tissues throughout your body that are not dehydrated. If this continues, dehydration spreads throughout the body. When a dehydrated person drinks water and rehydrates, the water is redistributed by the same gradient, but in the opposite direction, replenishing water in all of the tissues.

## Solute Movement between Compartments

The movement of some solutes between compartments is active, which consumes energy and is an active transport process, whereas the movement of other solutes is passive, which does not require energy. Active transport allows cells to move a specific substance against its concentration gradient through a membrane protein, requiring energy in the form of ATP. For example, the sodium-potassium pump employs active transport to pump sodium out of cells and potassium into cells, with both substances moving against their concentration gradients.

Passive transport of a molecule or ion depends on its ability to pass through the membrane, as well as the existence of a concentration gradient that allows the molecules to diffuse from an area of higher concentration to an area of lower concentration. Some molecules, like gases, lipids, and water itself (which also utilizes water channels in the membrane called aquaporins), slip fairly easily through the cell membrane; others, including polar molecules like glucose, amino acids, and ions do not. Some of these molecules enter and leave cells using facilitated transport, whereby the molecules move down a concentration gradient through specific protein channels in the membrane. This process does not require energy. For example, glucose is transferred into cells by glucose transporters that use facilitated transport (**Figure 26.8**).



**Figure 26.8 Facilitated Diffusion** Glucose molecules use facilitated diffusion to move down a concentration gradient through the carrier protein channels in the membrane. (credit: modification of work by Mariana Ruiz Villarreal)

## Disorders OF THE...

### Fluid Balance: Edema

Edema is the accumulation of excess water in the tissues. It is most common in the soft tissues of the extremities. The physiological causes of edema include water leakage from blood capillaries. Edema is almost always caused by an underlying medical condition, by the use of certain therapeutic drugs, by pregnancy, by localized injury, or by an allergic reaction. In the limbs, the symptoms of edema include swelling of the subcutaneous tissues, an increase in the normal size of the limb, and stretched, tight skin. One quick way to check for subcutaneous edema localized in a limb is to press a finger into the suspected area. Edema is likely if the depression persists for several seconds after the finger is removed (which is called “pitting”).

Pulmonary edema is excess fluid in the air sacs of the lungs, a common symptom of heart and/or kidney failure. People with pulmonary edema likely will experience difficulty breathing, and they may experience chest pain. Pulmonary edema can be life threatening, because it compromises gas exchange in the lungs, and anyone having symptoms should immediately seek medical care.

In pulmonary edema resulting from heart failure, excessive leakage of water occurs because fluids get “backed up” in the pulmonary capillaries of the lungs, when the left ventricle of the heart is unable to pump sufficient blood into the systemic circulation. Because the left side of the heart is unable to pump out its normal volume of blood, the blood in the pulmonary circulation gets “backed up,” starting with the left atrium, then into the pulmonary veins, and then into pulmonary capillaries. The resulting increased hydrostatic pressure within pulmonary capillaries, as blood is still coming in from the pulmonary arteries, causes fluid to be pushed out of them and into lung tissues.

Other causes of edema include damage to blood vessels and/or lymphatic vessels, or a decrease in osmotic pressure in chronic and severe liver disease, where the liver is unable to manufacture plasma proteins (**Figure 26.9**). A decrease in the normal levels of plasma proteins results in a decrease of colloid osmotic pressure (which counterbalances the hydrostatic pressure) in the capillaries. This process causes loss of water from the blood to the surrounding tissues, resulting in edema.



**Figure 26.9 Edema** An allergic reaction can cause capillaries in the hand to leak excess fluid that accumulates in the tissues. (credit: Jane Whitney)

Mild, transient edema of the feet and legs may be caused by sitting or standing in the same position for long periods of time, as in the work of a toll collector or a supermarket cashier. This is because deep veins in the lower limbs rely on skeletal muscle contractions to push on the veins and thus “pump” blood back to the heart. Otherwise, the venous blood pools in the lower limbs and can leak into surrounding tissues.

Medications that can result in edema include vasodilators, calcium channel blockers used to treat hypertension, non-

steroidal anti-inflammatory drugs, estrogen therapies, and some diabetes medications. Underlying medical conditions that can contribute to edema include congestive heart failure, kidney damage and kidney disease, disorders that affect the veins of the legs, and cirrhosis and other liver disorders.

Therapy for edema usually focuses on elimination of the cause. Activities that can reduce the effects of the condition include appropriate exercises to keep the blood and lymph flowing through the affected areas. Other therapies include elevation of the affected part to assist drainage, massage and compression of the areas to move the fluid out of the tissues, and decreased salt intake to decrease sodium and water retention.

## 26.2 | Water Balance

By the end of this section, you will be able to:

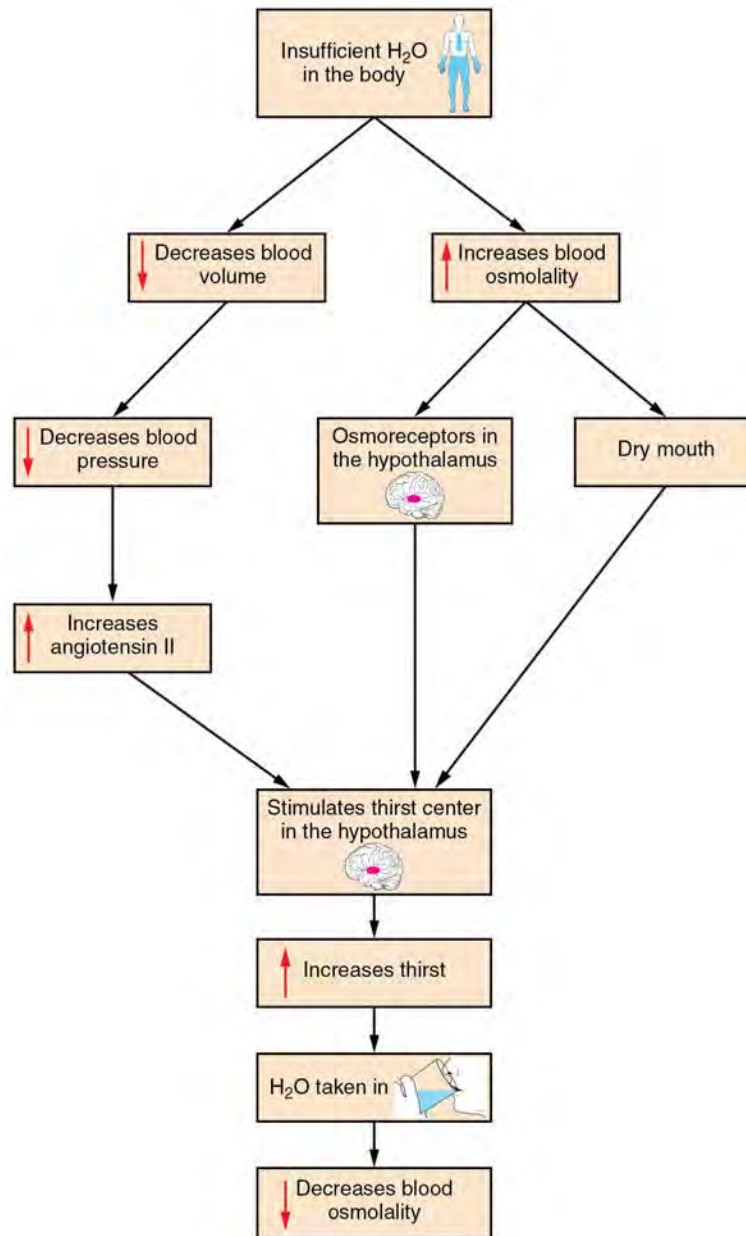
- Explain how water levels in the body influence the thirst cycle
- Identify the main route by which water leaves the body
- Describe the role of ADH and its effect on body water levels
- Define dehydration and identify common causes of dehydration

On a typical day, the average adult will take in about 2500 mL (almost 3 quarts) of aqueous fluids. Although most of the intake comes through the digestive tract, about 230 mL (8 ounces) per day is generated metabolically, in the last steps of aerobic respiration. Additionally, each day about the same volume (2500 mL) of water leaves the body by different routes; most of this lost water is removed as urine. The kidneys also can adjust blood volume through mechanisms that draw water out of the filtrate and urine. The kidneys can regulate water levels in the body; they conserve water if you are dehydrated, and they can make urine more dilute to expel excess water if necessary. Water is lost through the skin through evaporation from the skin surface without overt sweating and from air expelled from the lungs. This type of water loss is called insensible water loss because a person is usually unaware of it.

### Regulation of Water Intake

Osmolality is the ratio of solutes in a solution to a volume of solvent in a solution. **Plasma osmolality** is thus the ratio of solutes to water in blood plasma. A person's plasma osmolality value reflects his or her state of hydration. A healthy body maintains plasma osmolality within a narrow range, by employing several mechanisms that regulate both water intake and output.

Drinking water is considered voluntary. So how is water intake regulated by the body? Consider someone who is experiencing **dehydration**, a net loss of water that results in insufficient water in blood and other tissues. The water that leaves the body, as exhaled air, sweat, or urine, is ultimately extracted from blood plasma. As the blood becomes more concentrated, the thirst response—a sequence of physiological processes—is triggered (**Figure 26.10**). Osmoreceptors are sensory receptors in the thirst center in the hypothalamus that monitor the concentration of solutes (osmolality) of the blood. If blood osmolality increases above its ideal value, the hypothalamus transmits signals that result in a conscious awareness of thirst. The person should (and normally does) respond by drinking water. The hypothalamus of a dehydrated person also releases antidiuretic hormone (ADH) through the posterior pituitary gland. ADH signals the kidneys to recover water from urine, effectively diluting the blood plasma. To conserve water, the hypothalamus of a dehydrated person also sends signals via the sympathetic nervous system to the salivary glands in the mouth. The signals result in a decrease in watery, serous output (and an increase in stickier, thicker mucus output). These changes in secretions result in a “dry mouth” and the sensation of thirst.



**Figure 26.10 A Flowchart Showing the Thirst Response** The thirst response begins when osmoreceptors detect a decrease in water levels in the blood.

Decreased blood volume resulting from water loss has two additional effects. First, baroreceptors, blood-pressure receptors in the arch of the aorta and the carotid arteries in the neck, detect a decrease in blood pressure that results from decreased blood volume. The heart is ultimately signaled to increase its rate and/or strength of contractions to compensate for the lowered blood pressure.

Second, the kidneys have a renin-angiotensin hormonal system that increases the production of the active form of the hormone angiotensin II, which helps stimulate thirst, but also stimulates the release of the hormone aldosterone from the adrenal glands. Aldosterone increases the reabsorption of sodium in the distal tubules of the nephrons in the kidneys, and water follows this reabsorbed sodium back into the blood.

If adequate fluids are not consumed, dehydration results and a person's body contains too little water to function correctly. A person who repeatedly vomits or who has diarrhea may become dehydrated, and infants, because their body mass is so low, can become dangerously dehydrated very quickly. Endurance athletes such as distance runners often become dehydrated during long races. Dehydration can be a medical emergency, and a dehydrated person may lose consciousness, become

comatose, or die, if his or her body is not rehydrated quickly.

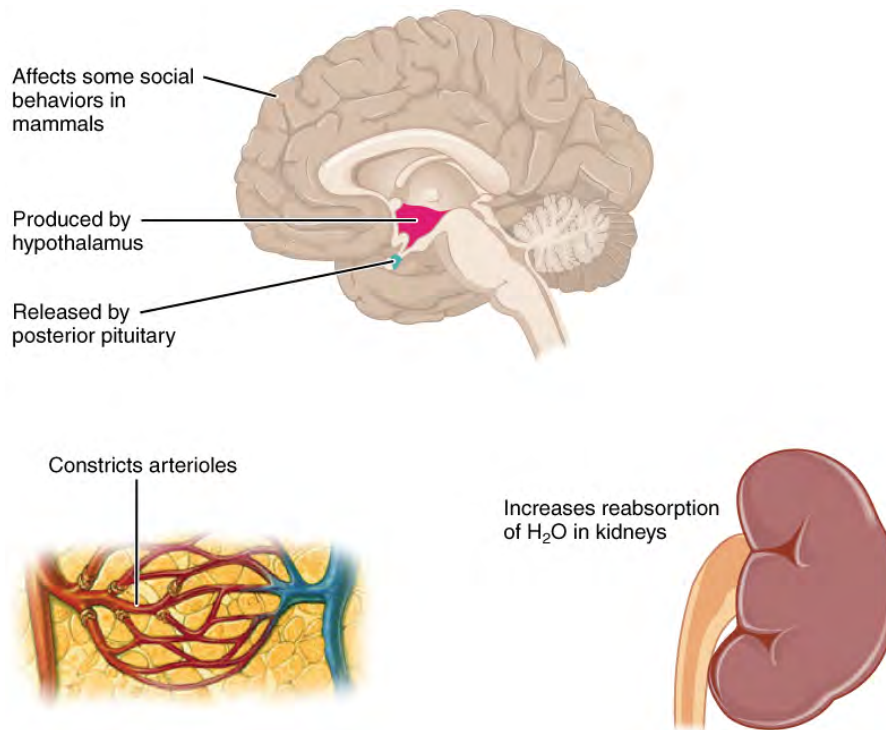
## Regulation of Water Output

Water loss from the body occurs predominantly through the renal system. A person produces an average of 1.5 liters (1.6 quarts) of urine per day. Although the volume of urine varies in response to hydration levels, there is a minimum volume of urine production required for proper bodily functions. The kidney excretes 100 to 1200 milliosmoles of solutes per day to rid the body of a variety of excess salts and other water-soluble chemical wastes, most notably creatinine, urea, and uric acid. Failure to produce the minimum volume of urine means that metabolic wastes cannot be effectively removed from the body, a situation that can impair organ function. The minimum level of urine production necessary to maintain normal function is about 0.47 liters (0.5 quarts) per day.

The kidneys also must make adjustments in the event of ingestion of too much fluid. **Diuresis**, which is the production of urine in excess of normal levels, begins about 30 minutes after drinking a large quantity of fluid. Diuresis reaches a peak after about 1 hour, and normal urine production is reestablished after about 3 hours.

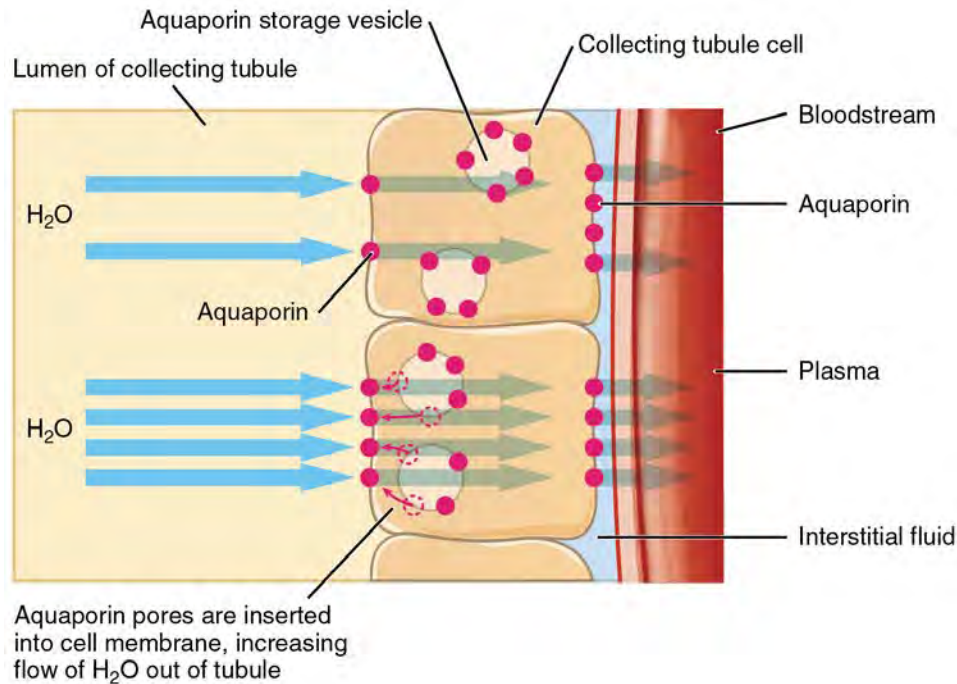
## Role of ADH

**Antidiuretic hormone (ADH)**, also known as vasopressin, controls the amount of water reabsorbed from the collecting ducts and tubules in the kidney. This hormone is produced in the hypothalamus and is delivered to the posterior pituitary for storage and release (**Figure 26.11**). When the osmoreceptors in the hypothalamus detect an increase in the concentration of blood plasma, the hypothalamus signals the release of ADH from the posterior pituitary into the blood.



**Figure 26.11 Antidiuretic Hormone (ADH)** ADH is produced in the hypothalamus and released by the posterior pituitary gland. It causes the kidneys to retain water, constricts arterioles in the peripheral circulation, and affects some social behaviors in mammals.

ADH has two major effects. It constricts the arterioles in the peripheral circulation, which reduces the flow of blood to the extremities and thereby increases the blood supply to the core of the body. ADH also causes the epithelial cells that line the renal collecting tubules to move water channel proteins, called aquaporins, from the interior of the cells to the apical surface, where these proteins are inserted into the cell membrane (**Figure 26.12**). The result is an increase in the water permeability of these cells and, thus, a large increase in water passage from the urine through the walls of the collecting tubules, leading to more reabsorption of water into the bloodstream. When the blood plasma becomes less concentrated and the level of ADH decreases, aquaporins are removed from collecting tubule cell membranes, and the passage of water out of urine and into the blood decreases.



**Figure 26.12 Aquaporins** The binding of ADH to receptors on the cells of the collecting tubule results in aquaporins being inserted into the plasma membrane, shown in the lower cell. This dramatically increases the flow of water out of the tubule and into the bloodstream.

A diuretic is a compound that increases urine output and therefore decreases water conservation by the body. Diuretics are used to treat hypertension, congestive heart failure, and fluid retention associated with menstruation. Alcohol acts as a diuretic by inhibiting the release of ADH. Additionally, caffeine, when consumed in high concentrations, acts as a diuretic.

## 26.3 | Electrolyte Balance

By the end of this section, you will be able to:

- List the role of the six most important electrolytes in the body
- Name the disorders associated with abnormally high and low levels of the six electrolytes
- Identify the predominant extracellular anion
- Describe the role of aldosterone on the level of water in the body

The body contains a large variety of ions, or electrolytes, which perform a variety of functions. Some ions assist in the transmission of electrical impulses along cell membranes in neurons and muscles. Other ions help to stabilize protein structures in enzymes. Still others aid in releasing hormones from endocrine glands. All of the ions in plasma contribute to the osmotic balance that controls the movement of water between cells and their environment.

Electrolytes in living systems include sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, copper, zinc, iron, manganese, molybdenum, copper, and chromium. In terms of body functioning, six electrolytes are most important: sodium, potassium, chloride, bicarbonate, calcium, and phosphate.

### Roles of Electrolytes

These six ions aid in nerve excitability, endocrine secretion, membrane permeability, buffering body fluids, and controlling the movement of fluids between compartments. These ions enter the body through the digestive tract. More than 90 percent of the calcium and phosphate that enters the body is incorporated into bones and teeth, with bone serving as a mineral reserve for these ions. In the event that calcium and phosphate are needed for other functions, bone tissue can be broken down to supply the blood and other tissues with these minerals. Phosphate is a normal constituent of nucleic acids; hence,

blood levels of phosphate will increase whenever nucleic acids are broken down.

Excretion of ions occurs mainly through the kidneys, with lesser amounts lost in sweat and in feces. Excessive sweating may cause a significant loss, especially of sodium and chloride. Severe vomiting or diarrhea will cause a loss of chloride and bicarbonate ions. Adjustments in respiratory and renal functions allow the body to regulate the levels of these ions in the ECF.

**Table 26.1** lists the reference values for blood plasma, cerebrospinal fluid (CSF), and urine for the six ions addressed in this section. In a clinical setting, sodium, potassium, and chloride are typically analyzed in a routine urine sample. In contrast, calcium and phosphate analysis requires a collection of urine across a 24-hour period, because the output of these ions can vary considerably over the course of a day. Urine values reflect the rates of excretion of these ions. Bicarbonate is the one ion that is not normally excreted in urine; instead, it is conserved by the kidneys for use in the body's buffering systems.

### Electrolyte and Ion Reference Values

Name	Chemical symbol	Plasma	CSF	Urine
Sodium	Na <sup>+</sup>	136.00–146.00 (mM)	138.00–150.00 (mM)	40.00–220.00 (mM)
Potassium	K <sup>+</sup>	3.50–5.00 (mM)	0.35–3.5 (mM)	25.00–125.00 (mM)
Chloride	Cl <sup>-</sup>	98.00–107.00 (mM)	118.00–132.00 (mM)	110.00–250.00 (mM)
Bicarbonate	HCO <sub>3</sub> <sup>-</sup>	22.00–29.00 (mM)	-----	-----
Calcium	Ca <sup>++</sup>	2.15–2.55 (mmol/day)	-----	Up to 7.49 (mmol/day)
Phosphate	HPO <sub>4</sub> <sup>2-</sup>	0.81–1.45 (mmol/day)	-----	12.90–42.00 (mmol/day)

**Table 26.1**

#### Sodium

Sodium is the major cation of the extracellular fluid. It is responsible for one-half of the osmotic pressure gradient that exists between the interior of cells and their surrounding environment. People eating a typical Western diet, which is very high in NaCl, routinely take in 130 to 160 mmol/day of sodium, but humans require only 1 to 2 mmol/day. This excess sodium appears to be a major factor in hypertension (high blood pressure) in some people. Excretion of sodium is accomplished primarily by the kidneys. Sodium is freely filtered through the glomerular capillaries of the kidneys, and although much of the filtered sodium is reabsorbed in the proximal convoluted tubule, some remains in the filtrate and urine, and is normally excreted.

**Hyponatremia** is a lower-than-normal concentration of sodium, usually associated with excess water accumulation in the body, which dilutes the sodium. An absolute loss of sodium may be due to a decreased intake of the ion coupled with its continual excretion in the urine. An abnormal loss of sodium from the body can result from several conditions, including excessive sweating, vomiting, or diarrhea; the use of diuretics; excessive production of urine, which can occur in diabetes; and acidosis, either metabolic acidosis or diabetic ketoacidosis.

A relative decrease in blood sodium can occur because of an imbalance of sodium in one of the body's other fluid compartments, like IF, or from a dilution of sodium due to water retention related to edema or congestive heart failure. At the cellular level, hyponatremia results in increased entry of water into cells by osmosis, because the concentration of solutes within the cell exceeds the concentration of solutes in the now-diluted ECF. The excess water causes swelling of the cells; the swelling of red blood cells—decreasing their oxygen-carrying efficiency and making them potentially too large to fit through capillaries—along with the swelling of neurons in the brain can result in brain damage or even death.

**Hypertatremia** is an abnormal increase of blood sodium. It can result from water loss from the blood, resulting in the hemoconcentration of all blood constituents. Hormonal imbalances involving ADH and aldosterone may also result in higher-than-normal sodium values.

#### Potassium

Potassium is the major intracellular cation. It helps establish the resting membrane potential in neurons and muscle fibers after membrane depolarization and action potentials. In contrast to sodium, potassium has very little effect on osmotic pressure. The low levels of potassium in blood and CSF are due to the sodium-potassium pumps in cell membranes,

which maintain the normal potassium concentration gradients between the ICF and ECF. The recommendation for daily intake/consumption of potassium is 4700 mg. Potassium is excreted, both actively and passively, through the renal tubules, especially the distal convoluted tubule and collecting ducts. Potassium participates in the exchange with sodium in the renal tubules under the influence of aldosterone, which also relies on basolateral sodium-potassium pumps.

**Hypokalemia** is an abnormally low potassium blood level. Similar to the situation with hyponatremia, hypokalemia can occur because of either an absolute reduction of potassium in the body or a relative reduction of potassium in the blood due to the redistribution of potassium. An absolute loss of potassium can arise from decreased intake, frequently related to starvation. It can also come about from vomiting, diarrhea, or alkalosis.

Some insulin-dependent diabetic patients experience a relative reduction of potassium in the blood from the redistribution of potassium. When insulin is administered and glucose is taken up by cells, potassium passes through the cell membrane along with glucose, decreasing the amount of potassium in the blood and IF, which can cause hyperpolarization of the cell membranes of neurons, reducing their responses to stimuli.

**Hyperkalemia**, an elevated potassium blood level, also can impair the function of skeletal muscles, the nervous system, and the heart. Hyperkalemia can result from increased dietary intake of potassium. In such a situation, potassium from the blood ends up in the ECF in abnormally high concentrations. This can result in a partial depolarization (excitation) of the plasma membrane of skeletal muscle fibers, neurons, and cardiac cells of the heart, and can also lead to an inability of cells to repolarize. For the heart, this means that it won't relax after a contraction, and will effectively "seize" and stop pumping blood, which is fatal within minutes. Because of such effects on the nervous system, a person with hyperkalemia may also exhibit mental confusion, numbness, and weakened respiratory muscles.

### Chloride

Chloride is the predominant extracellular anion. Chloride is a major contributor to the osmotic pressure gradient between the ICF and ECF, and plays an important role in maintaining proper hydration. Chloride functions to balance cations in the ECF, maintaining the electrical neutrality of this fluid. The paths of secretion and reabsorption of chloride ions in the renal system follow the paths of sodium ions.

**Hypochloremia**, or lower-than-normal blood chloride levels, can occur because of defective renal tubular absorption. Vomiting, diarrhea, and metabolic acidosis can also lead to hypochloremia. **Hyperchloremia**, or higher-than-normal blood chloride levels, can occur due to dehydration, excessive intake of dietary salt (NaCl) or swallowing of sea water, aspirin intoxication, congestive heart failure, and the hereditary, chronic lung disease, cystic fibrosis. In people who have cystic fibrosis, chloride levels in sweat are two to five times those of normal levels, and analysis of sweat is often used in the diagnosis of the disease.



Read this [article \(http://openstaxcollege.org/l/saltwater\)](http://openstaxcollege.org/l/saltwater) for an explanation of the effect of seawater on humans. What effect does drinking seawater have on the body?

### Bicarbonate

Bicarbonate is the second most abundant anion in the blood. Its principal function is to maintain your body's acid-base balance by being part of buffer systems. This role will be discussed in a different section.

Bicarbonate ions result from a chemical reaction that starts with carbon dioxide (CO<sub>2</sub>) and water, two molecules that are produced at the end of aerobic metabolism. Only a small amount of CO<sub>2</sub> can be dissolved in body fluids. Thus, over 90 percent of the CO<sub>2</sub> is converted into bicarbonate ions, HCO<sub>3</sub><sup>-</sup>, through the following reactions:



The bidirectional arrows indicate that the reactions can go in either direction, depending on the concentrations of the reactants and products. Carbon dioxide is produced in large amounts in tissues that have a high metabolic rate. Carbon dioxide is converted into bicarbonate in the cytoplasm of red blood cells through the action of an enzyme called carbonic anhydrase. Bicarbonate is transported in the blood. Once in the lungs, the reactions reverse direction, and  $\text{CO}_2$  is regenerated from bicarbonate to be exhaled as metabolic waste.

## Calcium

About two pounds of calcium in your body are bound up in bone, which provides hardness to the bone and serves as a mineral reserve for calcium and its salts for the rest of the tissues. Teeth also have a high concentration of calcium within them. A little more than one-half of blood calcium is bound to proteins, leaving the rest in its ionized form. Calcium ions,  $\text{Ca}^{2+}$ , are necessary for muscle contraction, enzyme activity, and blood coagulation. In addition, calcium helps to stabilize cell membranes and is essential for the release of neurotransmitters from neurons and of hormones from endocrine glands.

Calcium is absorbed through the intestines under the influence of activated vitamin D. A deficiency of vitamin D leads to a decrease in absorbed calcium and, eventually, a depletion of calcium stores from the skeletal system, potentially leading to rickets in children and osteomalacia in adults, contributing to osteoporosis.

**Hypocalcemia**, or abnormally low calcium blood levels, is seen in hypoparathyroidism, which may follow the removal of the thyroid gland, because the four nodules of the parathyroid gland are embedded in it. **Hypercalcemia**, or abnormally high calcium blood levels, is seen in primary hyperparathyroidism. Some malignancies may also result in hypercalcemia.

## Phosphate

Phosphate is present in the body in three ionic forms:  $\text{H}_2\text{PO}_4^-$ ,  $\text{HPO}_4^{2-}$ , and  $\text{PO}_4^{3-}$ . The most common form is  $\text{HPO}_4^{2-}$ . Bone and teeth bind up 85 percent of the body's phosphate as part of calcium-phosphate salts. Phosphate is found in phospholipids, such as those that make up the cell membrane, and in ATP, nucleotides, and buffers.

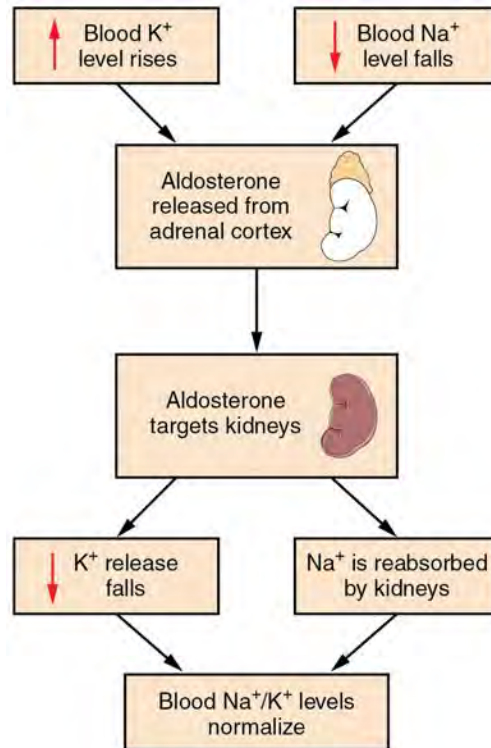
**Hypophosphatemia**, or abnormally low phosphate blood levels, occurs with heavy use of antacids, during alcohol withdrawal, and during malnourishment. In the face of phosphate depletion, the kidneys usually conserve phosphate, but during starvation, this conservation is impaired greatly. **Hyperphosphatemia**, or abnormally increased levels of phosphates in the blood, occurs if there is decreased renal function or in cases of acute lymphocytic leukemia. Additionally, because phosphate is a major constituent of the ICF, any significant destruction of cells can result in dumping of phosphate into the ECF.

## Regulation of Sodium and Potassium

Sodium is reabsorbed from the renal filtrate, and potassium is excreted into the filtrate in the renal collecting tubule. The control of this exchange is governed principally by two hormones—aldosterone and angiotensin II.

### Aldosterone

Recall that aldosterone increases the excretion of potassium and the reabsorption of sodium in the distal tubule. Aldosterone is released if blood levels of potassium increase, if blood levels of sodium severely decrease, or if blood pressure decreases. Its net effect is to conserve and increase water levels in the plasma by reducing the excretion of sodium, and thus water, from the kidneys. In a negative feedback loop, increased osmolality of the ECF (which follows aldosterone-stimulated sodium absorption) inhibits the release of the hormone (**Figure 26.13**).

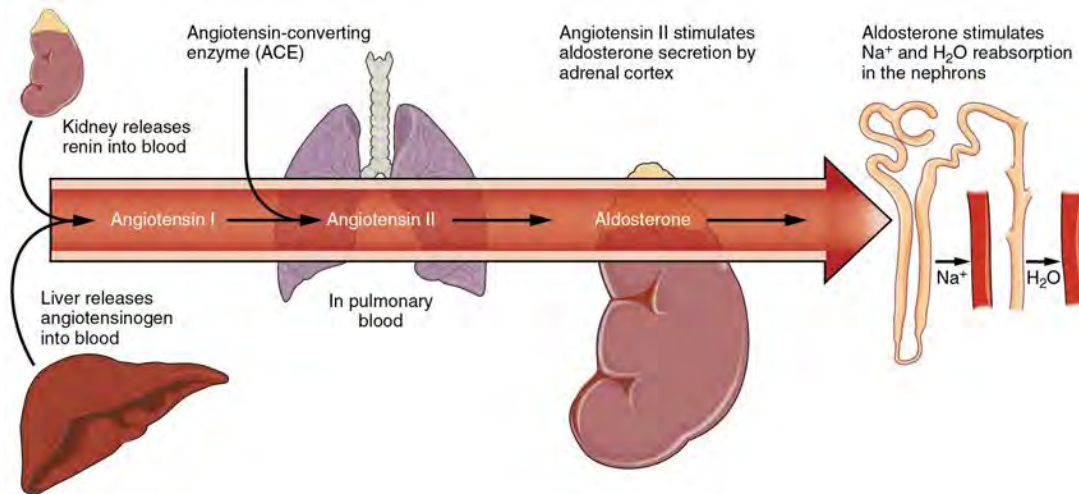


**Figure 26.13 The Aldosterone Feedback Loop** Aldosterone, which is released by the adrenal gland, facilitates reabsorption of Na<sup>+</sup> and thus the reabsorption of water.

### Angiotensin II

Angiotensin II causes vasoconstriction and an increase in systemic blood pressure. This action increases the glomerular filtration rate, resulting in more material filtered out of the glomerular capillaries and into Bowman's capsule. Angiotensin II also signals an increase in the release of aldosterone from the adrenal cortex.

In the distal convoluted tubules and collecting ducts of the kidneys, aldosterone stimulates the synthesis and activation of the sodium-potassium pump (Figure 26.14). Sodium passes from the filtrate, into and through the cells of the tubules and ducts, into the ECF and then into capillaries. Water follows the sodium due to osmosis. Thus, aldosterone causes an increase in blood sodium levels and blood volume. Aldosterone's effect on potassium is the reverse of that of sodium; under its influence, excess potassium is pumped into the renal filtrate for excretion from the body.



**Figure 26.14 The Renin-Angiotensin System** Angiotensin II stimulates the release of aldosterone from the adrenal cortex.

## Regulation of Calcium and Phosphate

Calcium and phosphate are both regulated through the actions of three hormones: parathyroid hormone (PTH), dihydroxyvitamin D (calcitriol), and calcitonin. All three are released or synthesized in response to the blood levels of calcium.

PTH is released from the parathyroid gland in response to a decrease in the concentration of blood calcium. The hormone activates osteoclasts to break down bone matrix and release inorganic calcium-phosphate salts. PTH also increases the gastrointestinal absorption of dietary calcium by converting vitamin D into **dihydroxyvitamin D** (calcitriol), an active form of vitamin D that intestinal epithelial cells require to absorb calcium.

PTH raises blood calcium levels by inhibiting the loss of calcium through the kidneys. PTH also increases the loss of phosphate through the kidneys.

Calcitonin is released from the thyroid gland in response to elevated blood levels of calcium. The hormone increases the activity of osteoblasts, which remove calcium from the blood and incorporate calcium into the bony matrix.

## 26.4 | Acid-Base Balance

By the end of this section, you will be able to:

- Identify the most powerful buffer system in the body
- Explain the way in which the respiratory system affects blood pH

Proper physiological functioning depends on a very tight balance between the concentrations of acids and bases in the blood. Acid-base balance is measured using the pH scale, as shown in **Figure 26.15**. A variety of buffering systems permits blood and other bodily fluids to maintain a narrow pH range, even in the face of perturbations. A buffer is a chemical system that prevents a radical change in fluid pH by dampening the change in hydrogen ion concentrations in the case of excess acid or base. Most commonly, the substance that absorbs the ions is either a weak acid, which takes up hydroxyl ions, or a weak base, which takes up hydrogen ions.

pH	Examples of solutions
0	Battery acid, strong hydrofluoric acid
1	Hydrochloric acid secreted by stomach lining
2	Lemon juice, gastric acid, vinegar
3	Grapefruit juice, orange juice, soda
4	Tomato juice, acid rain
5	Soft drinking water, black coffee
6	Urine, saliva
7	"Pure" water
8	Sea water
9	Baking soda
10	Great Salt Lake, milk of magnesia
11	Ammonia solution
12	Soapy water
13	Bleach, oven cleaner
14	Liquid drain cleaner

**Figure 26.15 The pH Scale** This chart shows where many common substances fall on the pH scale.

## Buffer Systems in the Body

The buffer systems in the human body are extremely efficient, and different systems work at different rates. It takes only seconds for the chemical buffers in the blood to make adjustments to pH. The respiratory tract can adjust the blood pH upward in minutes by exhaling CO<sub>2</sub> from the body. The renal system can also adjust blood pH through the excretion of hydrogen ions (H<sup>+</sup>) and the conservation of bicarbonate, but this process takes hours to days to have an effect.

The buffer systems functioning in blood plasma include plasma proteins, phosphate, and bicarbonate and carbonic acid buffers. The kidneys help control acid-base balance by excreting hydrogen ions and generating bicarbonate that helps maintain blood plasma pH within a normal range. Protein buffer systems work predominantly inside cells.

### Protein Buffers in Blood Plasma and Cells

Nearly all proteins can function as buffers. Proteins are made up of amino acids, which contain positively charged amino groups and negatively charged carboxyl groups. The charged regions of these molecules can bind hydrogen and hydroxyl ions, and thus function as buffers. Buffering by proteins accounts for two-thirds of the buffering power of the blood and most of the buffering within cells.

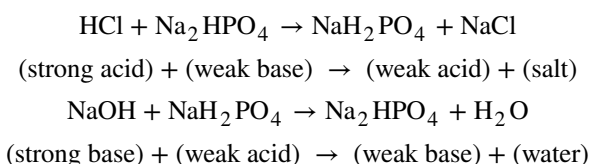
### Hemoglobin as a Buffer

Hemoglobin is the principal protein inside of red blood cells and accounts for one-third of the mass of the cell. During the

conversion of  $\text{CO}_2$  into bicarbonate, hydrogen ions liberated in the reaction are buffered by hemoglobin, which is reduced by the dissociation of oxygen. This buffering helps maintain normal pH. The process is reversed in the pulmonary capillaries to re-form  $\text{CO}_2$ , which then can diffuse into the air sacs to be exhaled into the atmosphere. This process is discussed in detail in the chapter on the respiratory system.

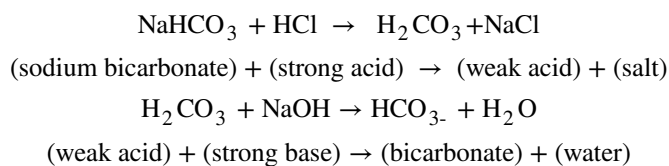
### Phosphate Buffer

Phosphates are found in the blood in two forms: sodium dihydrogen phosphate ( $\text{Na}_2\text{H}_2\text{PO}_4^-$ ), which is a weak acid, and sodium monohydrogen phosphate ( $\text{Na}_2\text{HPO}_4^{2-}$ ), which is a weak base. When  $\text{Na}_2\text{HPO}_4^{2-}$  comes into contact with a strong acid, such as HCl, the base picks up a second hydrogen ion to form the weak acid  $\text{Na}_2\text{H}_2\text{PO}_4^-$  and sodium chloride, NaCl. When  $\text{Na}_2\text{HPO}_4^{2-}$  (the weak acid) comes into contact with a strong base, such as sodium hydroxide (NaOH), the weak acid reverts back to the weak base and produces water. Acids and bases are still present, but they hold onto the ions.



### Bicarbonate-Carbonic Acid Buffer

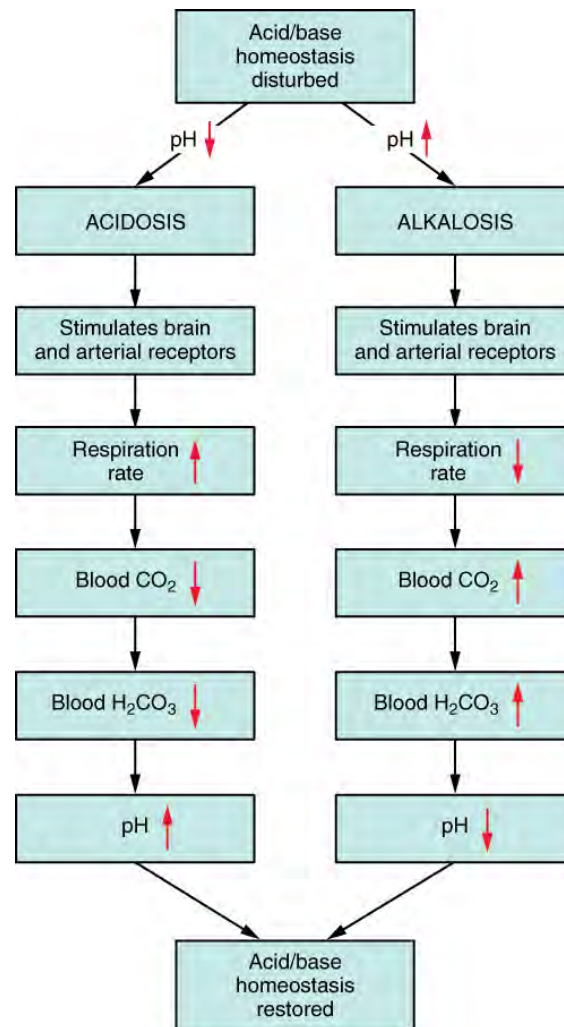
The bicarbonate-carbonic acid buffer works in a fashion similar to phosphate buffers. The bicarbonate is regulated in the blood by sodium, as are the phosphate ions. When sodium bicarbonate ( $\text{NaHCO}_3$ ), comes into contact with a strong acid, such as HCl, carbonic acid ( $\text{H}_2\text{CO}_3$ ), which is a weak acid, and NaCl are formed. When carbonic acid comes into contact with a strong base, such as NaOH, bicarbonate and water are formed.



As with the phosphate buffer, a weak acid or weak base captures the free ions, and a significant change in pH is prevented. Bicarbonate ions and carbonic acid are present in the blood in a 20:1 ratio if the blood pH is within the normal range. With 20 times more bicarbonate than carbonic acid, this capture system is most efficient at buffering changes that would make the blood more acidic. This is useful because most of the body's metabolic wastes, such as lactic acid and ketones, are acids. Carbonic acid levels in the blood are controlled by the expiration of  $\text{CO}_2$  through the lungs. In red blood cells, carbonic anhydrase forces the dissociation of the acid, rendering the blood less acidic. Because of this acid dissociation,  $\text{CO}_2$  is exhaled (see equations above). The level of bicarbonate in the blood is controlled through the renal system, where bicarbonate ions in the renal filtrate are conserved and passed back into the blood. However, the bicarbonate buffer is the primary buffering system of the IF surrounding the cells in tissues throughout the body.

## Respiratory Regulation of Acid-Base Balance

The respiratory system contributes to the balance of acids and bases in the body by regulating the blood levels of carbonic acid (**Figure 26.16**).  $\text{CO}_2$  in the blood readily reacts with water to form carbonic acid, and the levels of  $\text{CO}_2$  and carbonic acid in the blood are in equilibrium. When the  $\text{CO}_2$  level in the blood rises (as it does when you hold your breath), the excess  $\text{CO}_2$  reacts with water to form additional carbonic acid, lowering blood pH. Increasing the rate and/or depth of respiration (which you might feel the “urge” to do after holding your breath) allows you to exhale more  $\text{CO}_2$ . The loss of  $\text{CO}_2$  from the body reduces blood levels of carbonic acid and thereby adjusts the pH upward, toward normal levels. As you might have surmised, this process also works in the opposite direction. Excessive deep and rapid breathing (as in hyperventilation) rids the blood of  $\text{CO}_2$  and reduces the level of carbonic acid, making the blood too alkaline. This brief alkalosis can be remedied by rebreathing air that has been exhaled into a paper bag. Rebreathing exhaled air will rapidly bring blood pH down toward normal.



**Figure 26.16 Respiratory Regulation of Blood pH** The respiratory system can reduce blood pH by removing  $\text{CO}_2$  from the blood.

The chemical reactions that regulate the levels of  $\text{CO}_2$  and carbonic acid occur in the lungs when blood travels through the lung's pulmonary capillaries. Minor adjustments in breathing are usually sufficient to adjust the pH of the blood by changing how much  $\text{CO}_2$  is exhaled. In fact, doubling the respiratory rate for less than 1 minute, removing “extra”  $\text{CO}_2$ , would increase the blood pH by 0.2. This situation is common if you are exercising strenuously over a period of time. To keep up the necessary energy production, you would produce excess  $\text{CO}_2$  (and lactic acid if exercising beyond your aerobic threshold). In order to balance the increased acid production, the respiration rate goes up to remove the  $\text{CO}_2$ . This helps to keep you from developing acidosis.

The body regulates the respiratory rate by the use of chemoreceptors, which primarily use  $\text{CO}_2$  as a signal. Peripheral blood sensors are found in the walls of the aorta and carotid arteries. These sensors signal the brain to provide immediate adjustments to the respiratory rate if  $\text{CO}_2$  levels rise or fall. Yet other sensors are found in the brain itself. Changes in the pH of CSF affect the respiratory center in the medulla oblongata, which can directly modulate breathing rate to bring the pH back into the normal range.

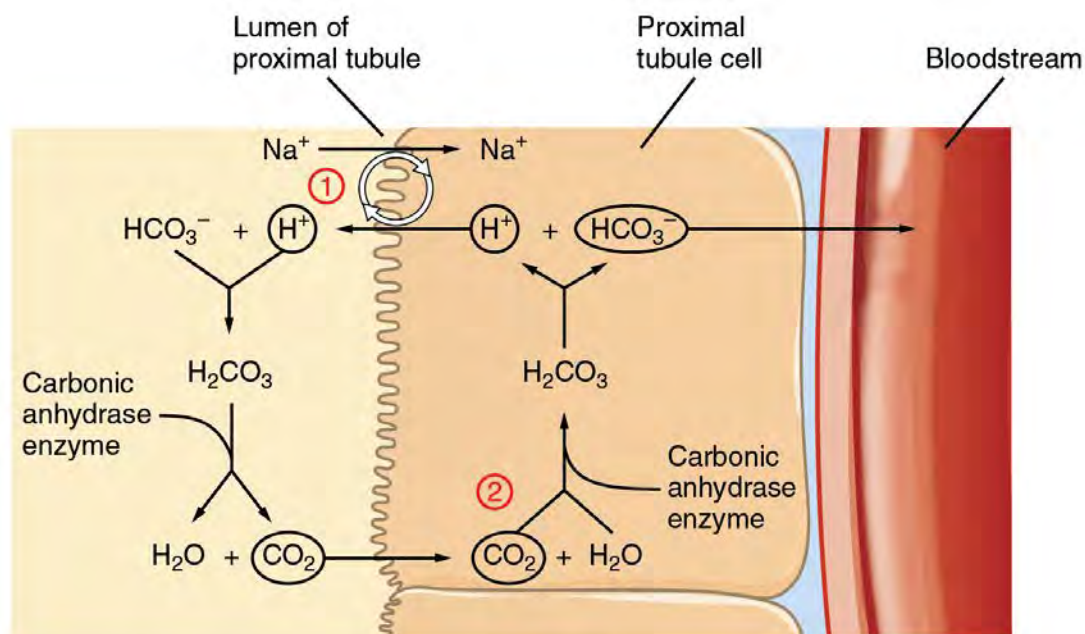
**Hypercapnia**, or abnormally elevated blood levels of  $\text{CO}_2$ , occurs in any situation that impairs respiratory functions, including pneumonia and congestive heart failure. Reduced breathing (hypoventilation) due to drugs such as morphine, barbiturates, or ethanol (or even just holding one's breath) can also result in hypercapnia. **Hypocapnia**, or abnormally low blood levels of  $\text{CO}_2$ , occurs with any cause of hyperventilation that drives off the  $\text{CO}_2$ , such as salicylate toxicity, elevated room temperatures, fever, or hysteria.

## Renal Regulation of Acid-Base Balance

The renal regulation of the body's acid-base balance addresses the metabolic component of the buffering system. Whereas the respiratory system (together with breathing centers in the brain) controls the blood levels of carbonic acid by controlling the exhalation of  $\text{CO}_2$ , the renal system controls the blood levels of bicarbonate. A decrease of blood bicarbonate can result from the inhibition of carbonic anhydrase by certain diuretics or from excessive bicarbonate loss due to diarrhea. Blood bicarbonate levels are also typically lower in people who have Addison's disease (chronic adrenal insufficiency), in which aldosterone levels are reduced, and in people who have renal damage, such as chronic nephritis. Finally, low bicarbonate blood levels can result from elevated levels of ketones (common in unmanaged diabetes mellitus), which bind bicarbonate in the filtrate and prevent its conservation.

Bicarbonate ions,  $\text{HCO}_3^-$ , found in the filtrate, are essential to the bicarbonate buffer system, yet the cells of the tubule are not permeable to bicarbonate ions. The steps involved in supplying bicarbonate ions to the system are seen in **Figure 26.17** and are summarized below:

- Step 1: Sodium ions are reabsorbed from the filtrate in exchange for  $\text{H}^+$  by an antiport mechanism in the apical membranes of cells lining the renal tubule.
- Step 2: The cells produce bicarbonate ions that can be shunted to peritubular capillaries.
- Step 3: When  $\text{CO}_2$  is available, the reaction is driven to the formation of carbonic acid, which dissociates to form a bicarbonate ion and a hydrogen ion.
- Step 4: The bicarbonate ion passes into the peritubular capillaries and returns to the blood. The hydrogen ion is secreted into the filtrate, where it can become part of new water molecules and be reabsorbed as such, or removed in the urine.



**Figure 26.17 Conservation of Bicarbonate in the Kidney** Tubular cells are not permeable to bicarbonate; thus, bicarbonate is conserved rather than reabsorbed. Steps 1 and 2 of bicarbonate conservation are indicated.

It is also possible that salts in the filtrate, such as sulfates, phosphates, or ammonia, will capture hydrogen ions. If this occurs, the hydrogen ions will not be available to combine with bicarbonate ions and produce  $\text{CO}_2$ . In such cases, bicarbonate ions are not conserved from the filtrate to the blood, which will also contribute to a pH imbalance and acidosis.

The hydrogen ions also compete with potassium to exchange with sodium in the renal tubules. If more potassium is present than normal, potassium, rather than the hydrogen ions, will be exchanged, and increased potassium enters the filtrate. When this occurs, fewer hydrogen ions in the filtrate participate in the conversion of bicarbonate into  $\text{CO}_2$  and less bicarbonate is conserved. If there is less potassium, more hydrogen ions enter the filtrate to be exchanged with sodium and more bicarbonate is conserved.

Chloride ions are important in neutralizing positive ion charges in the body. If chloride is lost, the body uses bicarbonate

ions in place of the lost chloride ions. Thus, lost chloride results in an increased reabsorption of bicarbonate by the renal system.

## Disorders OF THE...

### Acid-Base Balance: Ketoacidosis

Diabetic acidosis, or ketoacidosis, occurs most frequently in people with poorly controlled diabetes mellitus. When certain tissues in the body cannot get adequate amounts of glucose, they depend on the breakdown of fatty acids for energy. When acetyl groups break off the fatty acid chains, the acetyl groups then non-enzymatically combine to form ketone bodies, acetoacetic acid, beta-hydroxybutyric acid, and acetone, all of which increase the acidity of the blood. In this condition, the brain isn't supplied with enough of its fuel—glucose—to produce all of the ATP it requires to function.

Ketoacidosis can be severe and, if not detected and treated properly, can lead to diabetic coma, which can be fatal. A common early symptom of ketoacidosis is deep, rapid breathing as the body attempts to drive off CO<sub>2</sub> and compensate for the acidosis. Another common symptom is fruity-smelling breath, due to the exhalation of acetone. Other symptoms include dry skin and mouth, a flushed face, nausea, vomiting, and stomach pain. Treatment for diabetic coma is ingestion or injection of sugar; its prevention is the proper daily administration of insulin.

A person who is diabetic and uses insulin can initiate ketoacidosis if a dose of insulin is missed. Among people with type 2 diabetes, those of Hispanic and African-American descent are more likely to go into ketoacidosis than those of other ethnic backgrounds, although the reason for this is unknown.

## 26.5 | Disorders of Acid-Base Balance

By the end of this section, you will be able to:

- Identify the three blood variables considered when making a diagnosis of acidosis or alkalosis
- Identify the source of compensation for blood pH problems of a respiratory origin
- Identify the source of compensation for blood pH problems of a metabolic/renal origin

Normal arterial blood pH is restricted to a very narrow range of 7.35 to 7.45. A person who has a blood pH below 7.35 is considered to be in acidosis (actually, “physiological acidosis,” because blood is not truly acidic until its pH drops below 7), and a continuous blood pH below 7.0 can be fatal. Acidosis has several symptoms, including headache and confusion, and the individual can become lethargic and easily fatigued (**Figure 26.18**). A person who has a blood pH above 7.45 is considered to be in alkalosis, and a pH above 7.8 is fatal. Some symptoms of alkalosis include cognitive impairment (which can progress to unconsciousness), tingling or numbness in the extremities, muscle twitching and spasm, and nausea and vomiting. Both acidosis and alkalosis can be caused by either metabolic or respiratory disorders.

As discussed earlier in this chapter, the concentration of carbonic acid in the blood is dependent on the level of CO<sub>2</sub> in the body and the amount of CO<sub>2</sub> gas exhaled through the lungs. Thus, the respiratory contribution to acid-base balance is usually discussed in terms of CO<sub>2</sub> (rather than of carbonic acid). Remember that a molecule of carbonic acid is lost for every molecule of CO<sub>2</sub> exhaled, and a molecule of carbonic acid is formed for every molecule of CO<sub>2</sub> retained.

**SYMPTOMS OF ACIDOSIS****Central Nervous System**

Headache  
Sleepiness  
Confusion  
Loss of consciousness  
Coma

**Respiratory System**

Shortness of breath  
Coughing

**Heart**

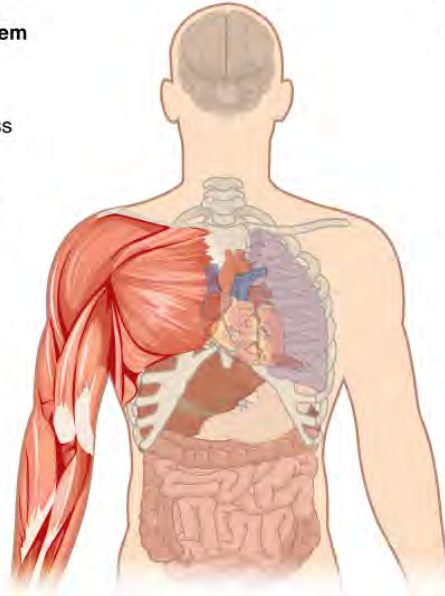
Arrhythmia  
Increased heart rate

**Muscular System**

Seizures  
Weakness

**Digestive System**

Nausea  
Vomiting  
Diarrhea

**SYMPTOMS OF ALKALOSIS****Central Nervous System**

Confusion  
Light-headedness  
Stupor  
Coma

**Peripheral Nervous System**

Hand tremor  
Numbness or tingling in  
the face, hands, or feet

**Muscular System**

Twitching  
Prolonged spasms

**Digestive System**

Nausea  
Vomiting

**Figure 26.18 Symptoms of Acidosis and Alkalosis** Symptoms of acidosis affect several organ systems. Both acidosis and alkalosis can be diagnosed using a blood test.

## Metabolic Acidosis: Primary Bicarbonate Deficiency

**Metabolic acidosis** occurs when the blood is too acidic (pH below 7.35) due to too little bicarbonate, a condition called primary bicarbonate deficiency. At the normal pH of 7.40, the ratio of bicarbonate to carbonic acid buffer is 20:1. If a person's blood pH drops below 7.35, then he or she is in metabolic acidosis. The most common cause of metabolic acidosis is the presence of organic acids or excessive ketones in the blood. **Table 26.2** lists some other causes of metabolic acidosis.

### Common Causes of Metabolic Acidosis and Blood Metabolites

Cause	Metabolite
Diarrhea	Bicarbonate
Uremia	Phosphoric, sulfuric, and lactic acids
Diabetic ketoacidosis	Increased ketones
Strenuous exercise	Lactic acid
Methanol	Formic acid*
Paraldehyde	$\beta$ -Hydroxybutyric acid*
Isopropanol	Propionic acid*
Ethylene glycol	Glycolic acid, and some oxalic and formic acids*
Salicylate/aspirin	Sulfasalicylic acid (SSA)*

**Table 26.2 \*Acid metabolites from ingested chemical.**

The first three of the eight causes of metabolic acidosis listed are medical (or unusual physiological) conditions. Strenuous exercise can cause temporary metabolic acidosis due to the production of lactic acid. The last five causes result from the ingestion of specific substances. The active form of aspirin is its metabolite, sulfasalicylic acid. An overdose of aspirin causes acidosis due to the acidity of this metabolite. Metabolic acidosis can also result from uremia, which is the retention of urea and uric acid. Metabolic acidosis can also arise from diabetic ketoacidosis, wherein an excess of ketones is present in the blood. Other causes of metabolic acidosis are a decrease in the excretion of hydrogen ions, which inhibits the

conservation of bicarbonate ions, and excessive loss of bicarbonate ions through the gastrointestinal tract due to diarrhea.

## Metabolic Alkalosis: Primary Bicarbonate Excess

**Metabolic alkalosis** is the opposite of metabolic acidosis. It occurs when the blood is too alkaline (pH above 7.45) due to too much bicarbonate (called primary bicarbonate excess).

A transient excess of bicarbonate in the blood can follow ingestion of excessive amounts of bicarbonate, citrate, or antacids for conditions such as stomach acid reflux—known as heartburn. Cushing’s disease, which is the chronic hypersecretion of adrenocorticotrophic hormone (ACTH) by the anterior pituitary gland, can cause chronic metabolic alkalosis. The oversecretion of ACTH results in elevated aldosterone levels and an increased loss of potassium by urinary excretion. Other causes of metabolic alkalosis include the loss of hydrochloric acid from the stomach through vomiting, potassium depletion due to the use of diuretics for hypertension, and the excessive use of laxatives.

## Respiratory Acidosis: Primary Carbonic Acid/CO<sub>2</sub> Excess

**Respiratory acidosis** occurs when the blood is overly acidic due to an excess of carbonic acid, resulting from too much CO<sub>2</sub> in the blood. Respiratory acidosis can result from anything that interferes with respiration, such as pneumonia, emphysema, or congestive heart failure.

## Respiratory Alkalosis: Primary Carbonic Acid/CO<sub>2</sub> Deficiency

**Respiratory alkalosis** occurs when the blood is overly alkaline due to a deficiency in carbonic acid and CO<sub>2</sub> levels in the blood. This condition usually occurs when too much CO<sub>2</sub> is exhaled from the lungs, as occurs in hyperventilation, which is breathing that is deeper or more frequent than normal. An elevated respiratory rate leading to hyperventilation can be due to extreme emotional upset or fear, fever, infections, hypoxia, or abnormally high levels of catecholamines, such as epinephrine and norepinephrine. Surprisingly, aspirin overdose—salicylate toxicity—can result in respiratory alkalosis as the body tries to compensate for initial acidosis.



Watch this [video \(http://openstaxcollege.org/l/altitude\)](http://openstaxcollege.org/l/altitude) to see a demonstration of the effect altitude has on blood pH. What effect does high altitude have on blood pH, and why?

## Compensation Mechanisms

Various compensatory mechanisms exist to maintain blood pH within a narrow range, including buffers, respiration, and renal mechanisms. Although compensatory mechanisms usually work very well, when one of these mechanisms is not working properly (like kidney failure or respiratory disease), they have their limits. If the pH and bicarbonate to carbonic acid ratio are changed too drastically, the body may not be able to compensate. Moreover, extreme changes in pH can denature proteins. Extensive damage to proteins in this way can result in disruption of normal metabolic processes, serious tissue damage, and ultimately death.

### Respiratory Compensation

Respiratory compensation for metabolic acidosis increases the respiratory rate to drive off CO<sub>2</sub> and readjust the bicarbonate to carbonic acid ratio to the 20:1 level. This adjustment can occur within minutes. Respiratory compensation for metabolic alkalosis is not as adept as its compensation for acidosis. The normal response of the respiratory system to elevated pH is to increase the amount of CO<sub>2</sub> in the blood by decreasing the respiratory rate to conserve CO<sub>2</sub>. There is a limit to the decrease in respiration, however, that the body can tolerate. Hence, the respiratory route is less efficient at compensating for

metabolic alkalosis than for acidosis.

### Metabolic Compensation

Metabolic and renal compensation for respiratory diseases that can create acidosis revolves around the conservation of bicarbonate ions. In cases of respiratory acidosis, the kidney increases the conservation of bicarbonate and secretion of  $H^+$  through the exchange mechanism discussed earlier. These processes increase the concentration of bicarbonate in the blood, reestablishing the proper relative concentrations of bicarbonate and carbonic acid. In cases of respiratory alkalosis, the kidneys decrease the production of bicarbonate and reabsorb  $H^+$  from the tubular fluid. These processes can be limited by the exchange of potassium by the renal cells, which use a  $K^+-H^+$  exchange mechanism (antiporter).

### Diagnosing Acidosis and Alkalosis

Lab tests for pH,  $CO_2$  partial pressure ( $pCO_2$ ), and  $HCO_3^-$  can identify acidosis and alkalosis, indicating whether the imbalance is respiratory or metabolic, and the extent to which compensatory mechanisms are working. The blood pH value, as shown in **Table 26.3**, indicates whether the blood is in acidosis, the normal range, or alkalosis. The  $pCO_2$  and total  $HCO_3^-$  values aid in determining whether the condition is metabolic or respiratory, and whether the patient has been able to compensate for the problem. **Table 26.3** lists the conditions and laboratory results that can be used to classify these conditions. Metabolic acid-base imbalances typically result from kidney disease, and the respiratory system usually responds to compensate.

#### Types of Acidosis and Alkalosis

	pH	$pCO_2$	Total $HCO_3^-$
Metabolic acidosis	↓	N, then ↓	↓
Respiratory acidosis	↓	↑	N, then ↑
Metabolic alkalosis	↑	N, then ↑	↑
Respiratory alkalosis	↑	↓	N, then ↓

**Table 26.3 Reference values (arterial): pH: 7.35–7.45;  $pCO_2$ : male: 35–48 mm Hg, female: 32–45 mm Hg; total venous bicarbonate: 22–29 mM. N denotes normal; ↑ denotes a rising or increased value; and ↓ denotes a falling or decreased value.**

Metabolic acidosis is problematic, as lower-than-normal amounts of bicarbonate are present in the blood. The  $pCO_2$  would be normal at first, but if compensation has occurred, it would decrease as the body reestablishes the proper ratio of bicarbonate and carbonic acid/ $CO_2$ .

Respiratory acidosis is problematic, as excess  $CO_2$  is present in the blood. Bicarbonate levels would be normal at first, but if compensation has occurred, they would increase in an attempt to reestablish the proper ratio of bicarbonate and carbonic acid/ $CO_2$ .

Alkalosis is characterized by a higher-than-normal pH. Metabolic alkalosis is problematic, as elevated pH and excess bicarbonate are present. The  $pCO_2$  would again be normal at first, but if compensation has occurred, it would increase as the body attempts to reestablish the proper ratios of bicarbonate and carbonic acid/ $CO_2$ .

Respiratory alkalosis is problematic, as  $CO_2$  deficiency is present in the bloodstream. The bicarbonate concentration would be normal at first. When renal compensation occurs, however, the bicarbonate concentration in blood decreases as the kidneys attempt to reestablish the proper ratios of bicarbonate and carbonic acid/ $CO_2$  by eliminating more bicarbonate to bring the pH into the physiological range.

## KEY TERMS

**antidiuretic hormone (ADH)** also known as vasopressin, a hormone that increases the volume of water reabsorbed from the collecting tubules of the kidney

**dehydration** state of containing insufficient water in blood and other tissues

**dihydroxyvitamin D** active form of vitamin D required by the intestinal epithelial cells for the absorption of calcium

**diuresis** excess production of urine

**extracellular fluid (ECF)** fluid exterior to cells; includes the interstitial fluid, blood plasma, and fluids found in other reservoirs in the body

**fluid compartment** fluid inside all cells of the body constitutes a compartment system that is largely segregated from other systems

**hydrostatic pressure** pressure exerted by a fluid against a wall, caused by its own weight or pumping force

**hypercalcemia** abnormally increased blood levels of calcium

**hypercapnia** abnormally elevated blood levels of CO<sub>2</sub>

**hyperchloremia** higher-than-normal blood chloride levels

**hyperkalemia** higher-than-normal blood potassium levels

**hyponatremia** abnormal increase in blood sodium levels

**hyperphosphatemia** abnormally increased blood phosphate levels

**hypocalcemia** abnormally low blood levels of calcium

**hypocapnia** abnormally low blood levels of CO<sub>2</sub>

**hypochloremia** lower-than-normal blood chloride levels

**hypokalemia** abnormally decreased blood levels of potassium

**hyponatremia** lower-than-normal levels of sodium in the blood

**hypophosphatemia** abnormally low blood phosphate levels

**interstitial fluid (IF)** fluid in the small spaces between cells not contained within blood vessels

**intracellular fluid (ICF)** fluid in the cytosol of cells

**metabolic acidosis** condition wherein a deficiency of bicarbonate causes the blood to be overly acidic

**metabolic alkalosis** condition wherein an excess of bicarbonate causes the blood to be overly alkaline

**plasma osmolality** ratio of solutes to a volume of solvent in the plasma; plasma osmolality reflects a person's state of hydration

**respiratory acidosis** condition wherein an excess of carbonic acid or CO<sub>2</sub> causes the blood to be overly acidic

**respiratory alkalosis** condition wherein a deficiency of carbonic acid/CO<sub>2</sub> levels causes the blood to be overly alkaline

## CHAPTER REVIEW

### 26.1 Body Fluids and Fluid Compartments

Your body is mostly water. Body fluids are aqueous solutions with differing concentrations of materials, called solutes. An appropriate balance of water and solute concentrations must be maintained to ensure cellular functions. If the cytosol becomes too concentrated due to water loss, cell functions deteriorate. If the cytosol becomes too dilute due to water intake by cells, cell membranes can be damaged, and the cell can burst. Hydrostatic pressure is the force exerted by a fluid against a wall and causes movement of fluid between compartments. Fluid can also move between compartments along an osmotic gradient. Active transport processes require ATP to move some solutes against their concentration gradients between compartments. Passive transport of a molecule or ion depends on its ability to pass easily through the membrane, as well as the existence of a high to low concentration gradient.

### 26.2 Water Balance

Homeostasis requires that water intake and output be balanced. Most water intake comes through the digestive tract via liquids and food, but roughly 10 percent of water available to the body is generated at the end of aerobic respiration during cellular metabolism. Urine produced by the kidneys accounts for the largest amount of water leaving the body. The kidneys can adjust the concentration of the urine to reflect the body's water needs, conserving water if the body is dehydrated or making urine more dilute to expel excess water when necessary. ADH is a hormone that helps the body to retain water by increasing water reabsorption by the kidneys.

### 26.3 Electrolyte Balance

Electrolytes serve various purposes, such as helping to conduct electrical impulses along cell membranes in neurons and muscles, stabilizing enzyme structures, and releasing hormones from endocrine glands. The ions in plasma also contribute to the osmotic balance that controls the movement of water between cells and their environment. Imbalances of these ions can result in various problems in the body, and their concentrations are tightly regulated. Aldosterone and angiotensin II control the exchange of sodium and potassium between the renal filtrate and the renal collecting tubule. Calcium and phosphate are regulated by PTH, calcitriol, and calcitonin.

### 26.4 Acid-Base Balance

A variety of buffering systems exist in the body that helps maintain the pH of the blood and other fluids within a narrow range—between pH 7.35 and 7.45. A buffer is a substance that prevents a radical change in fluid pH by absorbing excess hydrogen or hydroxyl ions. Most commonly, the substance that absorbs the ion is either a weak acid, which takes up a hydroxyl ion ( $\text{OH}^-$ ), or a weak base, which takes up a hydrogen ion ( $\text{H}^+$ ). Several substances serve as buffers in the body, including cell and plasma proteins, hemoglobin, phosphates, bicarbonate ions, and carbonic acid. The bicarbonate buffer is the primary buffering system of the IF surrounding the cells in tissues throughout the body. The respiratory and renal systems also play major roles in acid-base homeostasis by removing  $\text{CO}_2$  and hydrogen ions, respectively, from the body.

### 26.5 Disorders of Acid-Base Balance

Acidosis and alkalosis describe conditions in which a person's blood is, respectively, too acidic (pH below 7.35) and too alkaline (pH above 7.45). Each of these conditions can be caused either by metabolic problems related to bicarbonate levels or by respiratory problems related to carbonic acid and  $\text{CO}_2$  levels. Several compensatory mechanisms allow the body to maintain a normal pH.

## INTERACTIVE LINK QUESTIONS

1. Watch this **video** (<http://openstaxcollege.org/l/bodyfluids>) to learn more about body fluids, fluid compartments, and electrolytes. When blood volume decreases due to sweating, from what source is water taken in by the blood?
2. Watch this **video** (<http://openstaxcollege.org/l/dynamicfluid>) to see an explanation of the dynamics of fluid in the body's compartments. What happens in tissues when capillary blood pressure is less than osmotic pressure?
3. Read this **article** (<http://openstaxcollege.org/l/saltwater>) for an explanation of the effect of seawater on humans. What effect does drinking seawater have on the body?

4. Watch this [video \(http://openstaxcollege.org/l/altitude\)](http://openstaxcollege.org/l/altitude) to see a demonstration of the effect altitude has on blood pH. What effect does high altitude have on blood pH, and why?

## REVIEW QUESTIONS

5. Solute contributes to the movement of water between cells and the surrounding medium by \_\_\_\_\_.
- osmotic pressure
  - hydrostatic pressure
  - Brownian movement
  - random motion
6. A cation has a(n) \_\_\_\_\_ charge.
- neutral
  - positive
  - alternating
  - negative
7. Interstitial fluid (IF) is \_\_\_\_\_.
- the fluid in the cytosol of the cells
  - the fluid component of blood
  - the fluid that bathes all of the body's cells except for blood cells
  - the intracellular fluids found between membranes
8. The largest amount of water comes into the body via \_\_\_\_\_.
- metabolism
  - foods
  - liquids
  - humidified air
9. The largest amount of water leaves the body via \_\_\_\_\_.
- the GI tract
  - the skin as sweat
  - expiration
  - urine
10. Insensible water loss is water lost via \_\_\_\_\_.
- skin evaporation and in air from the lungs
  - urine
  - excessive sweating
  - vomiting or diarrhea
11. How soon after drinking a large glass of water will a person start increasing their urine output?
- 5 minutes
  - 30 minutes
  - 1 hour
  - 3 hours
12. Bone serves as a mineral reserve for which two ions?
- sodium and potassium
  - calcium and phosphate
  - chloride and bicarbonate
  - calcium and bicarbonate
13. Electrolytes are lost mostly through \_\_\_\_\_.
- renal function
  - sweating
  - feces
  - respiration
14. The major cation in extracellular fluid is \_\_\_\_\_.
- sodium
  - potassium
  - chloride
  - bicarbonate
15. The major cation in intracellular fluid is \_\_\_\_\_.
- sodium
  - potassium
  - chloride
  - bicarbonate
16. The major anion in extracellular fluid is \_\_\_\_\_.
- sodium
  - potassium
  - chloride
  - bicarbonate
17. Most of the body's calcium is found in \_\_\_\_\_.
- teeth
  - bone
  - plasma
  - extracellular fluids
18. Abnormally increased blood levels of sodium are termed \_\_\_\_\_.
- hyperkalemia
  - hyperchloremia
  - hyponatremia
  - hypercalcemia
19. The ion with the lowest blood level is \_\_\_\_\_.
- sodium
  - potassium
  - chloride
  - bicarbonate
20. Which two ions are most affected by aldosterone?
- sodium and potassium
  - chloride and bicarbonate
  - calcium and phosphate
  - sodium and phosphate

- 21.** Which of the following is the most important buffer inside red blood cells?
- plasma proteins
  - hemoglobin
  - phosphate buffers
  - bicarbonate: carbonic acid buffer
- 22.** Which explanation best describes why plasma proteins can function as buffers?
- Plasma proteins combine with bicarbonate to make a stronger buffer.
  - Plasma proteins are immune to damage from acids.
  - Proteins have both positive and negative charges on their surface.
  - Proteins are alkaline.
- 23.** The buffer that is adjusted to control acid-base balance is \_\_\_\_\_.
- plasma protein
  - hemoglobin
  - phosphate buffer
  - bicarbonate: carbonic acid buffer
- 24.** Carbonic acid levels are controlled through the \_\_\_\_\_.
- respiratory system
  - renal system
  - digestive system
  - metabolic rate of cells
- 25.** Bicarbonate ion concentrations in the blood are controlled through the \_\_\_\_\_.
- respiratory system
  - renal system
  - digestive system
  - metabolic rate of cells
- 26.** Which reaction is catalyzed by carbonic anhydrase?
- $\text{HPO}_4^{2-} + \text{H}^+ \leftrightarrow \text{H}_2\text{PO}_4^-$
  - $\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3$
  - $\text{H}_2\text{PO}_4^- + \text{OH}^- \leftrightarrow \text{HPO}_4^{2-} + \text{H}_2\text{O}$
  - $\text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+$
- 27.** Which of the following is a cause of metabolic acidosis?
- excessive HCl loss
  - increased aldosterone
  - diarrhea
  - prolonged use of diuretics
- 28.** Which of the following is a cause of respiratory acidosis?
- emphysema
  - low blood  $\text{K}^+$
  - increased aldosterone
  - increased blood ketones
- 29.** At a pH of 7.40, the carbonic acid ratio is \_\_\_\_\_.
- 35:1
  - 4:1
  - 20:1
  - 3:1
- 30.** Which of the following is characterized as metabolic alkalosis?
- increased pH, decreased  $\text{pCO}_2$ , decreased  $\text{HCO}_3^-$
  - increased pH, increased  $\text{pCO}_2$ , increased  $\text{HCO}_3^-$
  - decreased pH, decreased  $\text{pCO}_2$ , decreased  $\text{HCO}_3^-$
  - decreased pH, increased  $\text{pCO}_2$ , increased  $\text{HCO}_3^-$

## CRITICAL THINKING QUESTIONS

- 31.** Plasma contains more sodium than chloride. How can this be if individual ions of sodium and chloride exactly balance each other out, and plasma is electrically neutral?
- 32.** How is fluid moved from compartment to compartment?
- 33.** Describe the effect of ADH on renal collecting tubules.
- 34.** Why is it important for the amount of water intake to equal the amount of water output?
- 35.** Explain how the  $\text{CO}_2$  generated by cells and exhaled in the lungs is carried as bicarbonate in the blood.
- 36.** How can one have an imbalance in a substance, but not actually have elevated or deficient levels of that substance in the body?
- 37.** Describe the conservation of bicarbonate ions in the renal system.
- 38.** Describe the control of blood carbonic acid levels through the respiratory system.
- 39.** Case Study: Bob is a 64-year-old male admitted to the emergency room for asthma. His laboratory results are as follows: pH 7.31,  $\text{pCO}_2$  higher than normal, and total  $\text{HCO}_3^-$  also higher than normal. Classify his acid-base balance as acidosis or alkalosis, and as metabolic or respiratory. Is there evidence of compensation? Propose the mechanism by which asthma contributed to the lab results seen.
- 40.** Case Study: Kim is a 38-year-old women admitted to the hospital for bulimia. Her laboratory results are as follows: pH 7.48,  $\text{pCO}_2$  in the normal range, and total  $\text{HCO}_3^-$  higher than normal. Classify her acid-base balance as acidosis or alkalosis, and as metabolic or respiratory. Is there evidence of compensation? Propose the mechanism by which bulimia contributed to the lab results seen.

