# Anatomy & Physiology

## Volume 3 of 3: Chapters 22 - 28 of 28

## Textbook Equity Edition

**An Open Education Resource**

This multi-part Textbook Equity edition retains the original academic content as published by Openstax College, and under the terms of their Creative Commons license (CC-BY).


Fearlessly copy, print, remix[tm]


ISBN: 978-1-304-84331-9

Original published as "Anatomy and Physiology" by:

**OpenStax College**
Rice University
6100 Main Street MS-380
Houston, Texas 77005

To learn more about OpenStax College, visit http://openstaxcollege.org.
Individual print copies and bulk orders can be purchased through our website.



**ISBN-10** **1938168135**
**ISBN-13** **978-1-938168-13-0**
**Revision** **AP-1-001-DW**

**Textbook Equity Edition Vol 3**
License: CC-BY
ISBN: 978-1-304-84331-9

# Table of Contents

# 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 $CO_2$
- 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**).

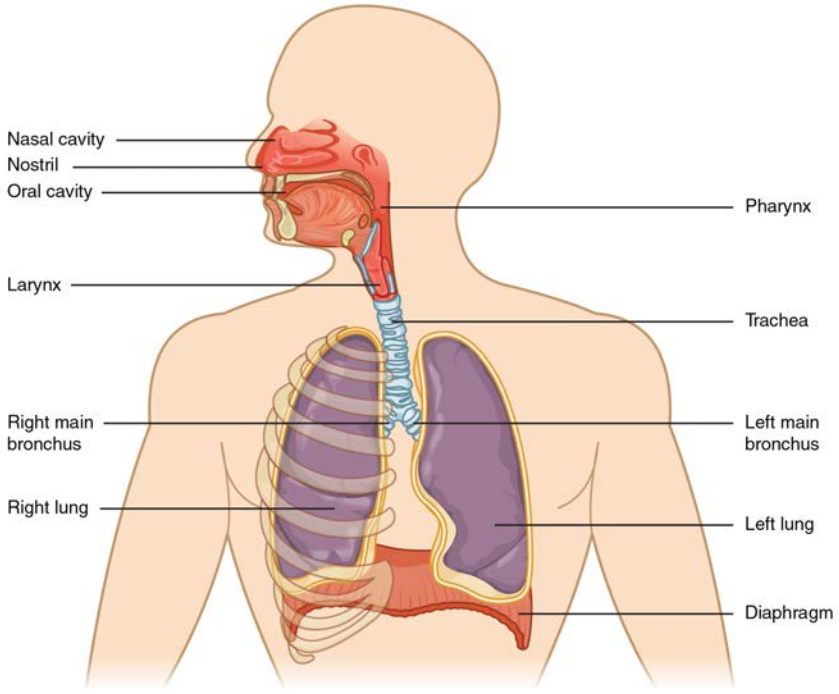



**Figure 22.2 Major Respiratory Structures** The major respiratory structures span the nasal cavity to the diaphragm.

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.

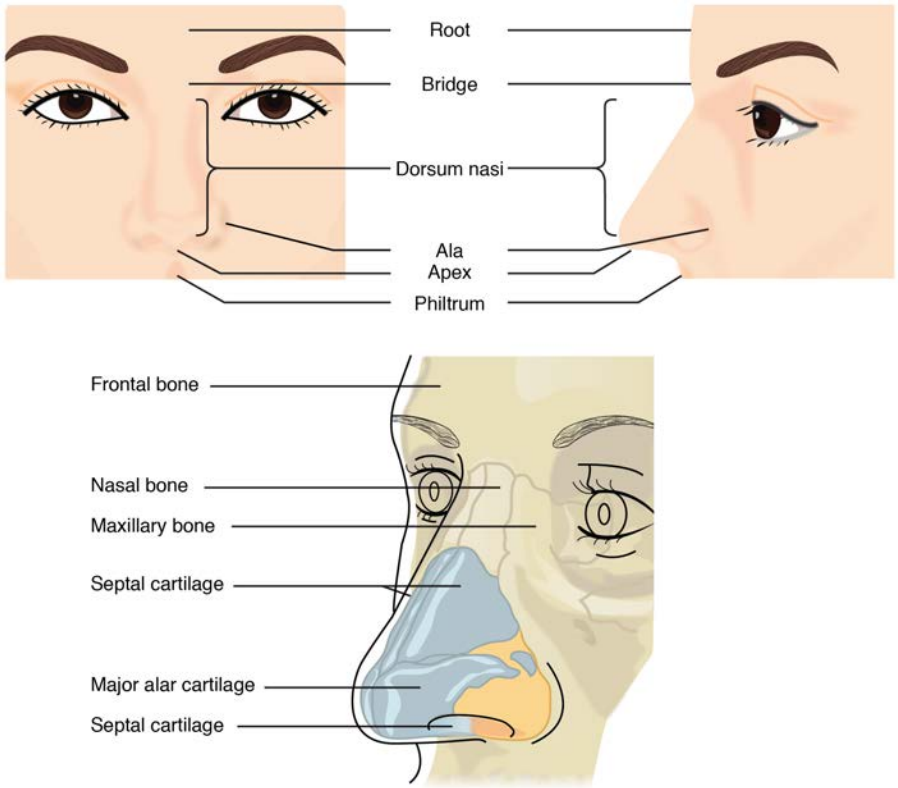



**Figure 22.3 Nose** This illustration shows features of the external nose (top) and skeletal features of the nose (bottom).

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.

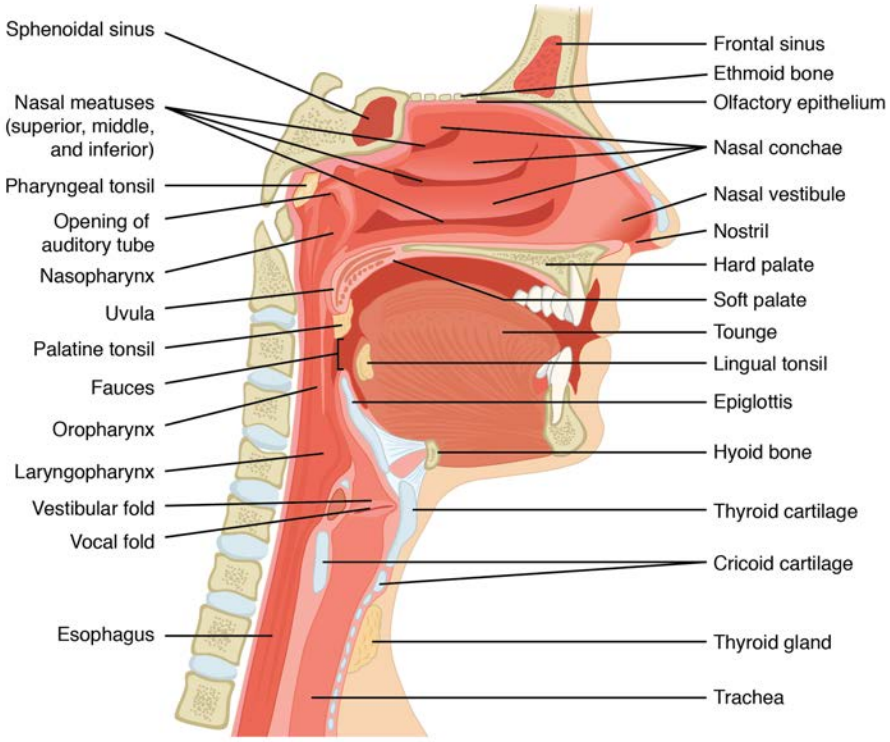



**Figure 22.4 Upper Airway**

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.

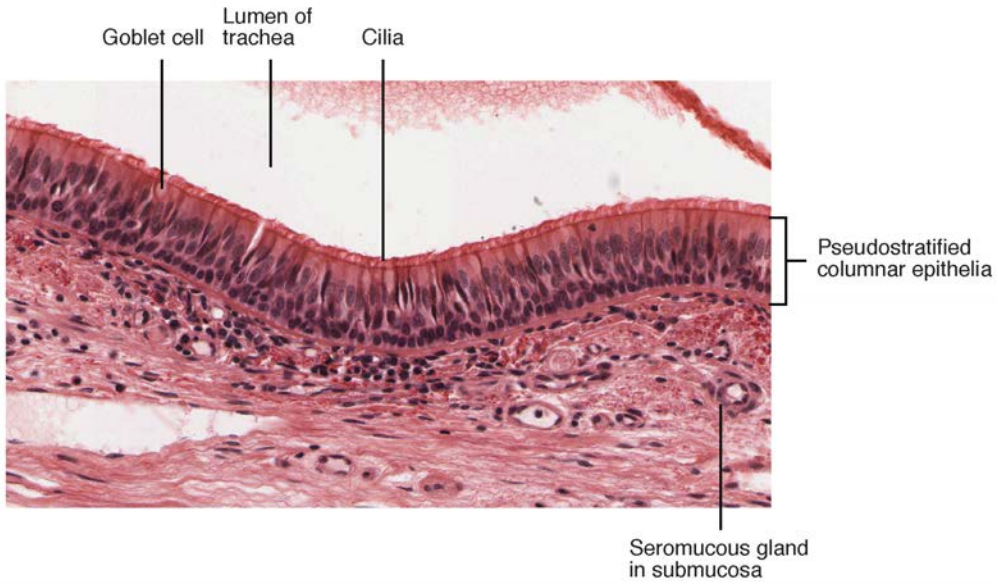



**Figure 22.5 Pseudostratified Ciliated Columnar Epithelium** Respiratory epithelium is pseudostratified ciliated columnar epithelium. Seromucous glands provide lubricating mucus. LM × 680. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

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://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**).

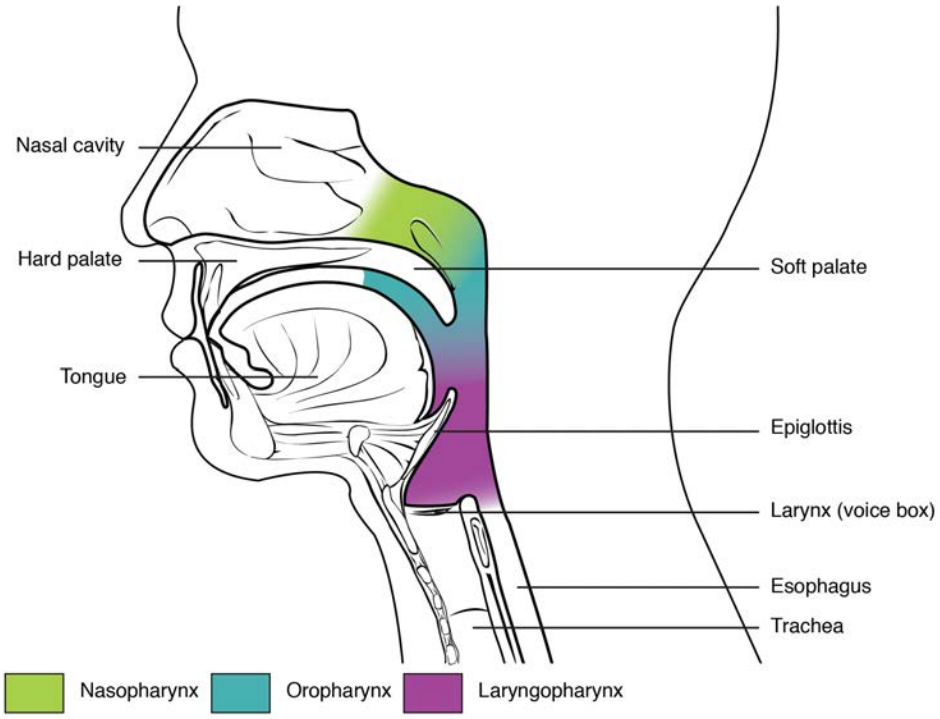



**Figure 22.6 Divisions of the Pharynx** The pharynx is divided into three regions: the nasopharynx, the oropharynx, and the laryngopharynx.

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.

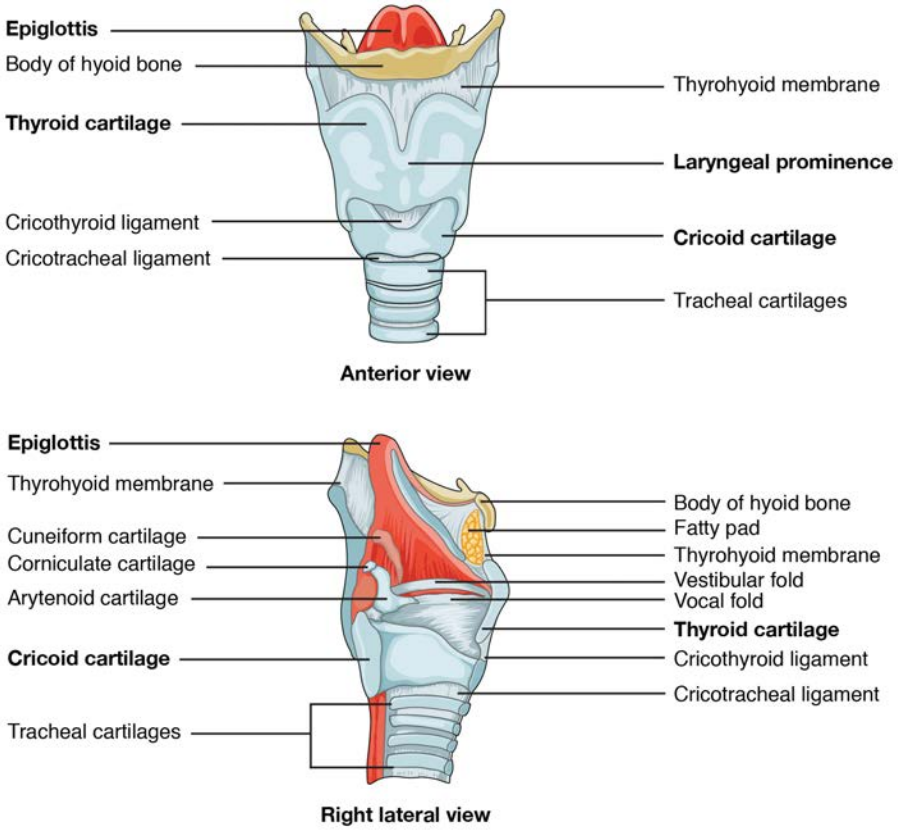



**Figure 22.7 Larynx** The larynx extends from the laryngopharynx and the hyoid bone to the trachea.

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.

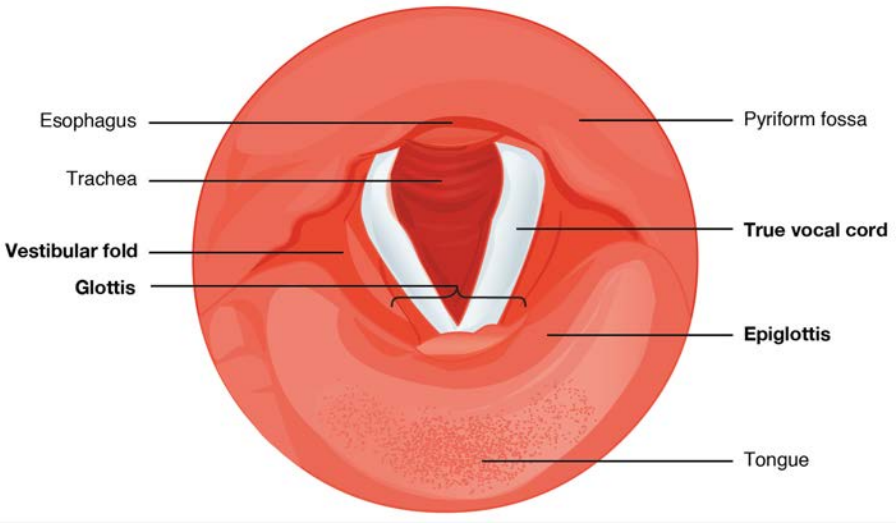



**Figure 22.8 Vocal Cords** The true vocal cords and vestibular folds of the larynx are viewed inferiorly from the laryngopharynx.

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.

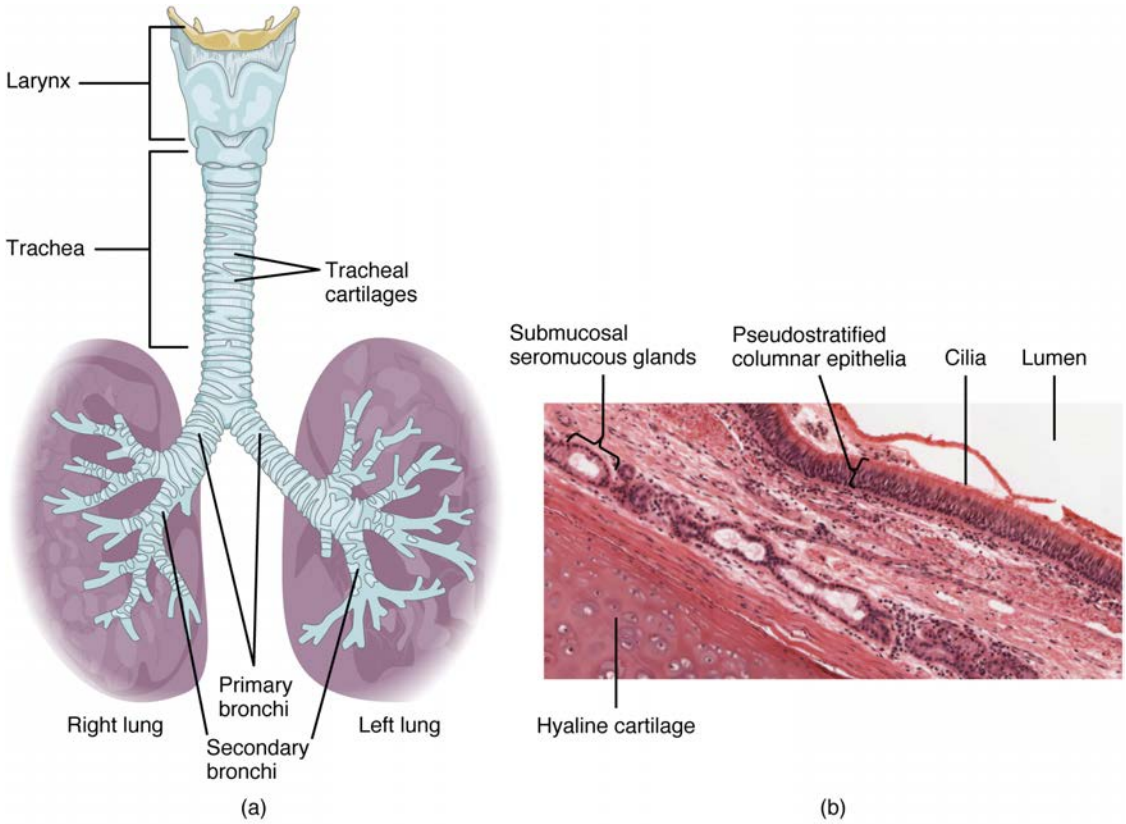



**Figure 22.9 Trachea** (a) The tracheal tube is formed by stacked, C-shaped pieces of hyaline cartilage. (b) The layer visible in this cross-section of tracheal wall tissue between the hyaline cartilage and the lumen of the trachea is the mucosa, which is composed of pseudostratified ciliated columnar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

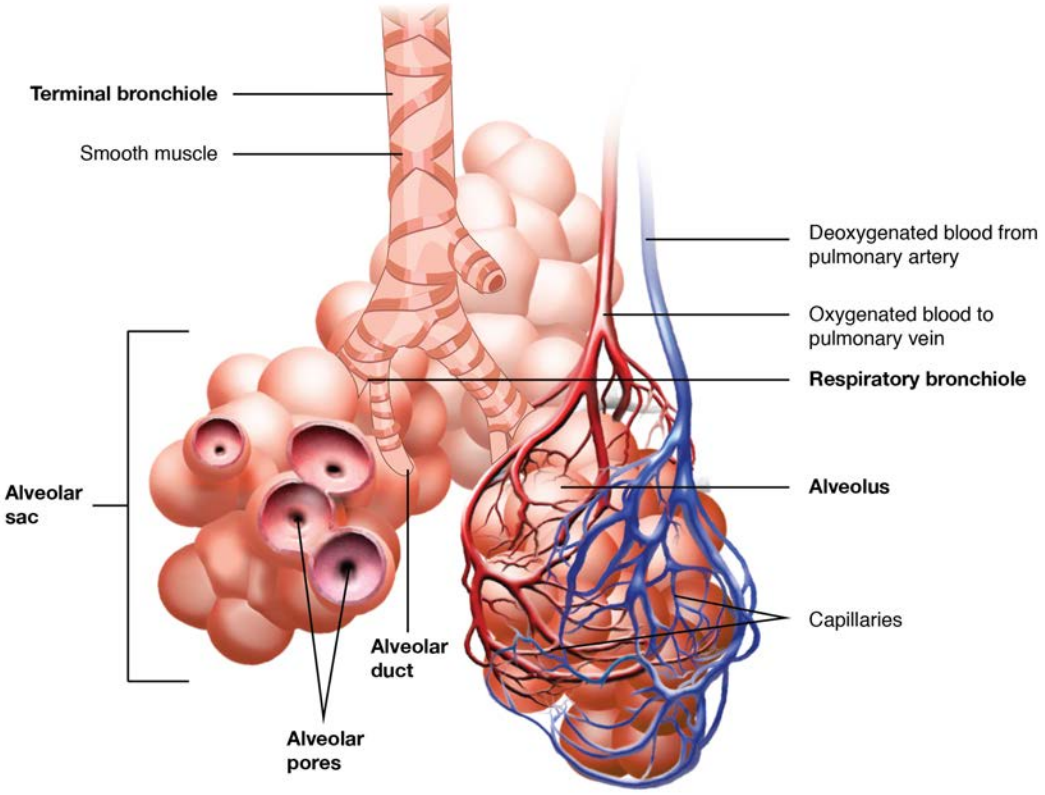



**Figure 22.10 Respiratory Zone** Bronchioles lead to alveolar sacs in the respiratory zone, where gas exchange occurs.

## 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 mm 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**).

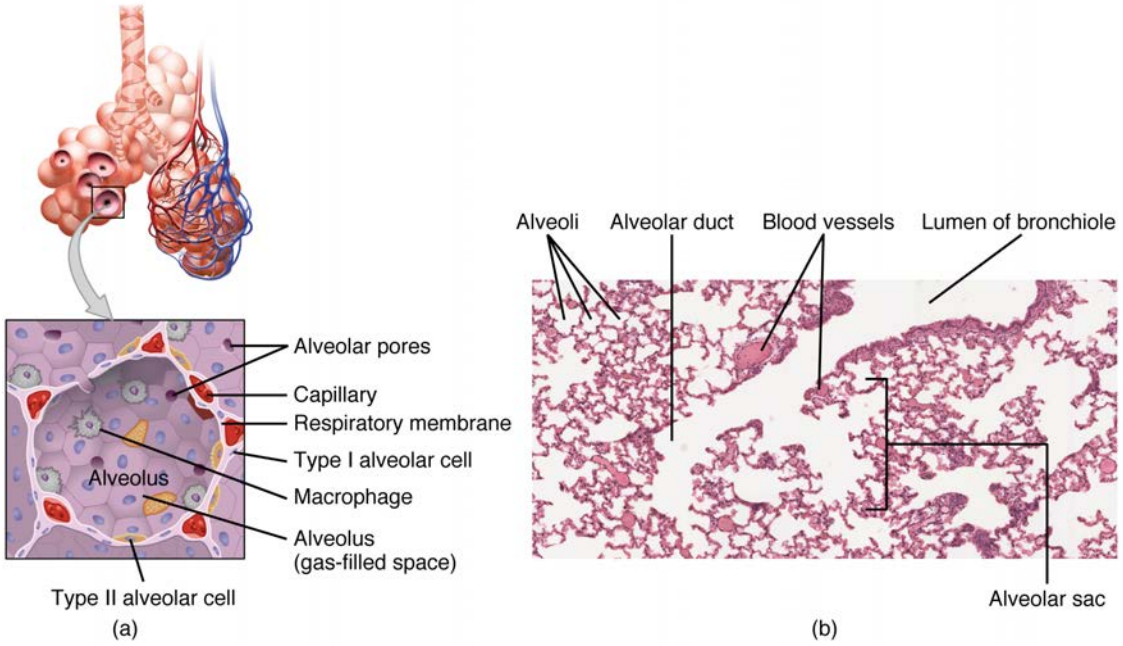



**Figure 22.11 Structures of the Respiratory Zone** (a) The alveolus is responsible for gas exchange. (b) A micrograph shows the alveolar structures within lung tissue. LM × 178. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

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 $CO_2$ to be released into the air of the alveoli.

Diseases OF THE...

## Respiratory System: Asthma

Asthma is 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.

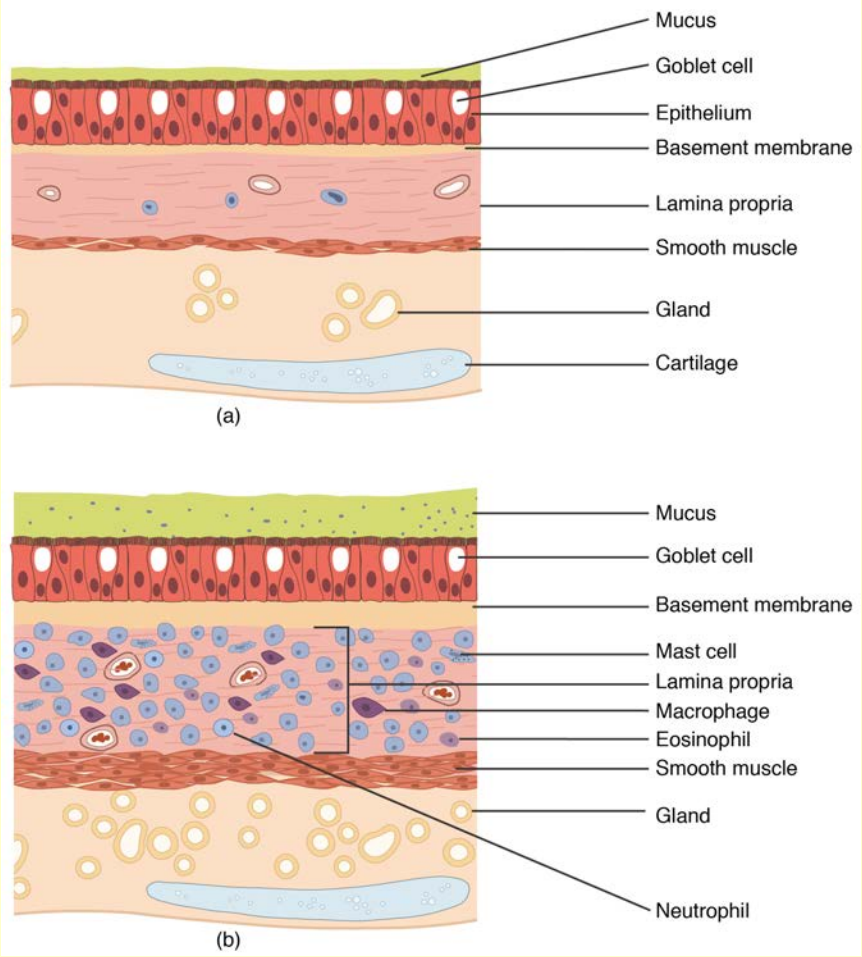



**Figure 22.12 Normal and Bronchial Asthma Tissues** (a) Normal lung tissue does not have the characteristics of lung tissue during (b) an asthma attack, which include thickened mucosa, increased mucus-producing goblet cells, and eosinophil infiltrates.

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)** 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.

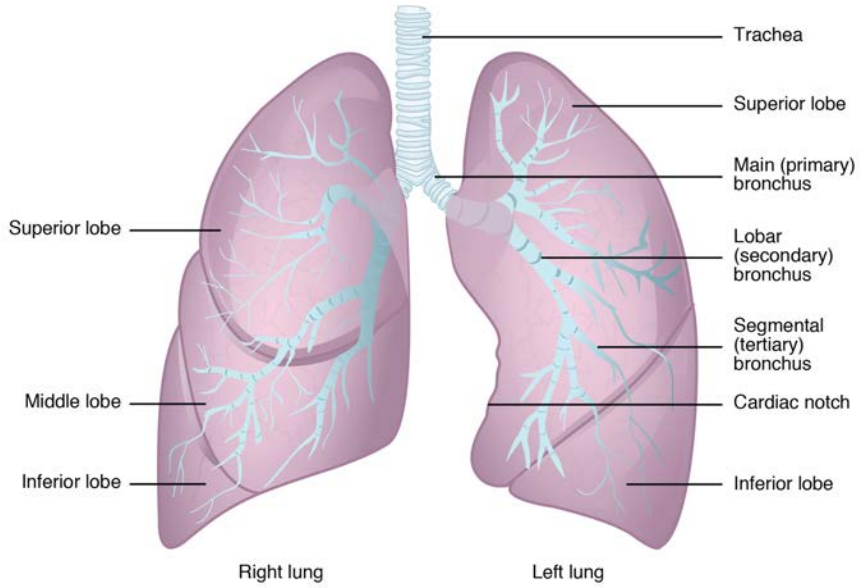



**Figure 22.13 Gross Anatomy of the Lungs**

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 the 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.

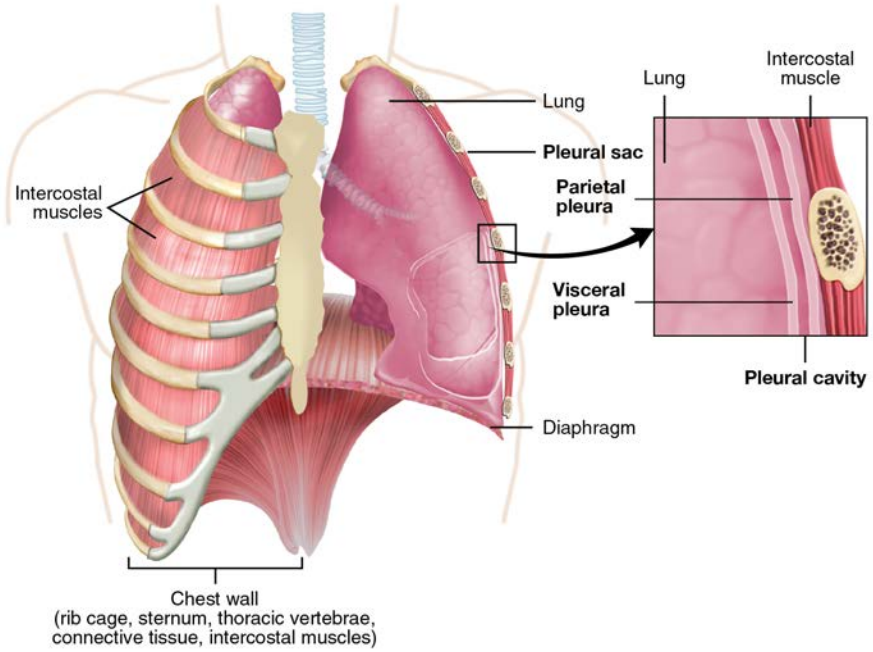



**Figure 22.14 Parietal and Visceral Pleurae of the Lungs**

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 polyaromatic 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 ($P_{atm}$); the air pressure within the alveoli, called alveolar pressure ($P_{alv}$); and the pressure within the pleural cavity, called intrapleural pressure ($P_{ip}$).

## Mechanisms of Breathing

The 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).

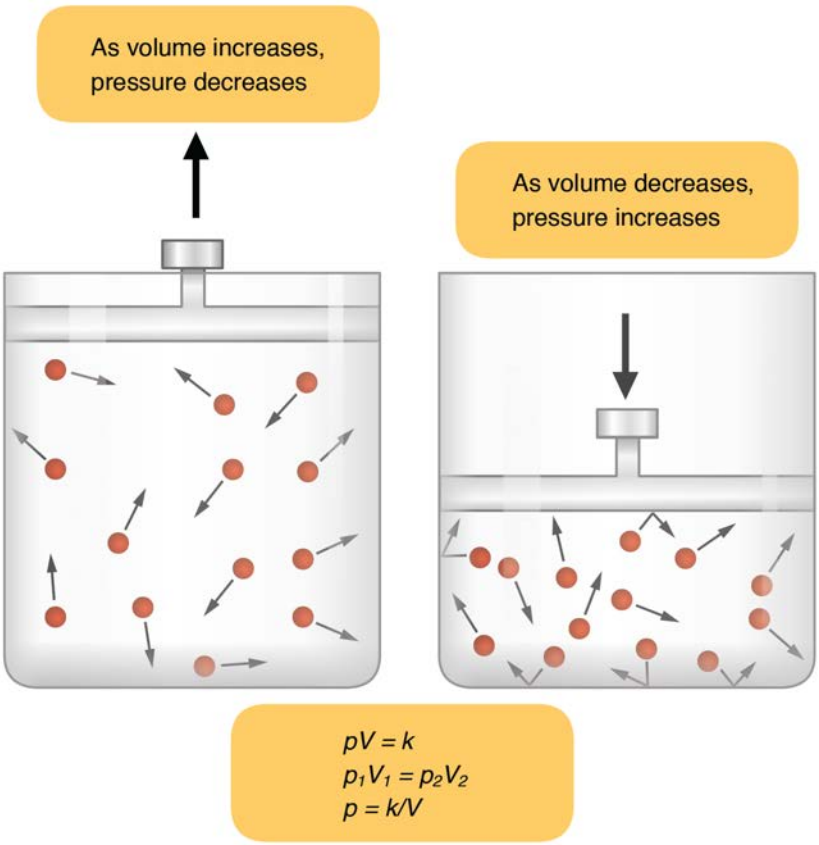



**Figure 22.15 Boyle's Law** In a gas, pressure increases as volume decreases.

Pulmonary ventilation is dependent on three types of pressure: atmospheric, intra-alveolar, and interpleural. **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 it is greater than the atmospheric pressure. A pressure that is equal to the atmospheric pressure is expressed as zero.

**Intra-alveolar 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 interpulmonary pressure of the alveoli always equalizes with the atmospheric pressure.

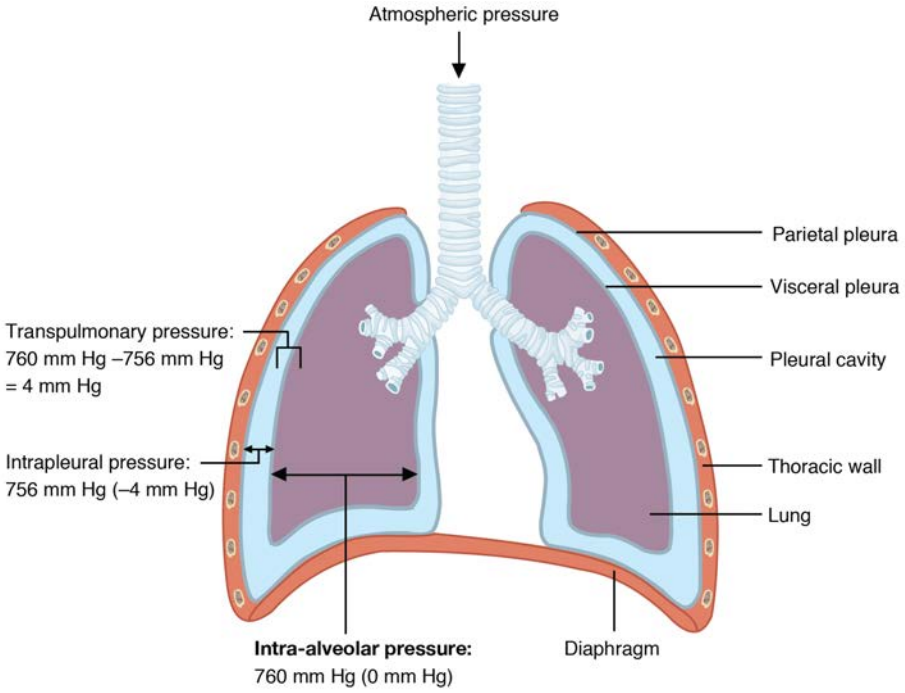



**Figure 22.16 Intrapulmonary and Intrapleural Pressure Relationships** Alveolar pressure changes during the different phases of the cycle. It equalizes at 760 mm Hg but does not remain at 760 mm Hg.

**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.

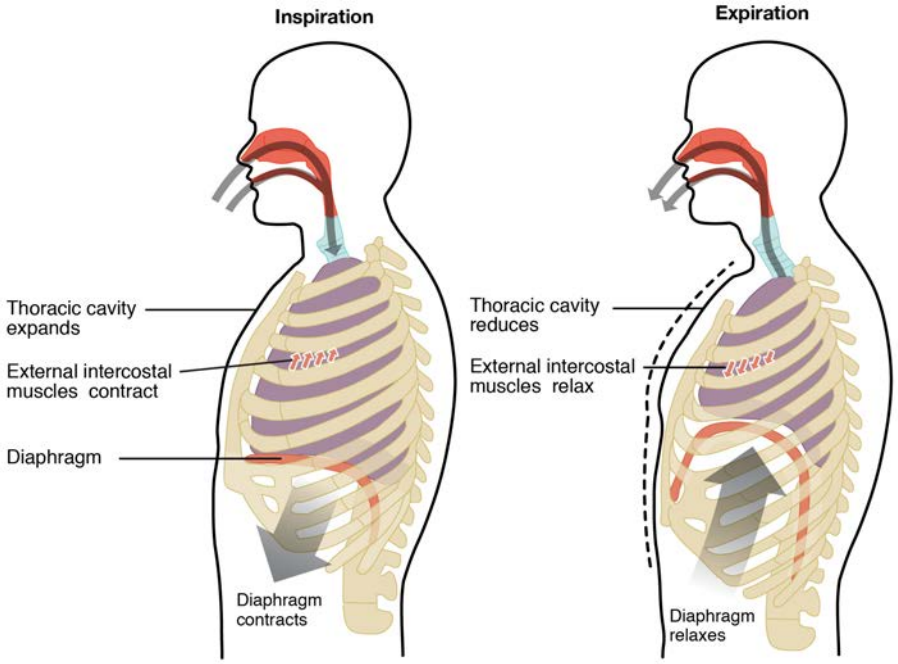



**Figure 22.17 Inspiration and Expiration** Inspiration and expiration occur due to the expansion and contraction of the thoracic cavity, respectively.

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 interpulmonary pressure. The interpulmonary 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).

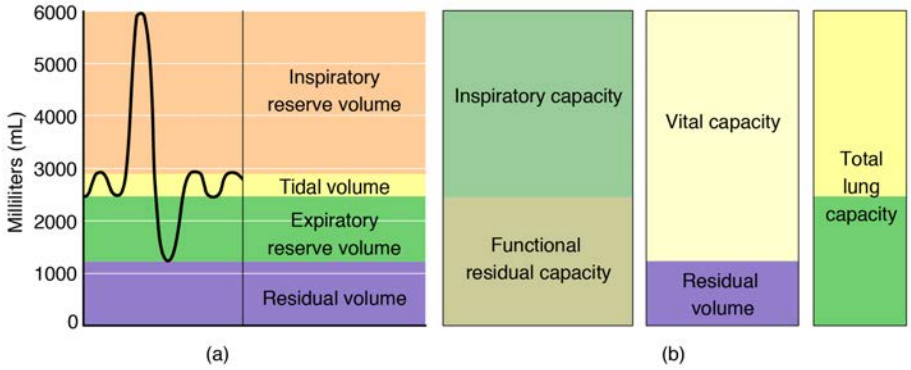



**Figure 22.18 Respiratory Volumes and Capacities** These two graphs show (a) respiratory volumes and (b) the combination of volumes that results in respiratory capacity.

| 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 in one 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).

## Interactive LINK


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 renter | 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 $PCO_2$, $PO_2$, and pH |
| Carotid body | Monitors blood $PCO_2$, $PO_2$, and pH |
| Hypothalamus | Monitors emotional state and body temperature |

Table 22.1

## Summary of Ventilation Regulation

| System component | Function |
|---|---|
| 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**).

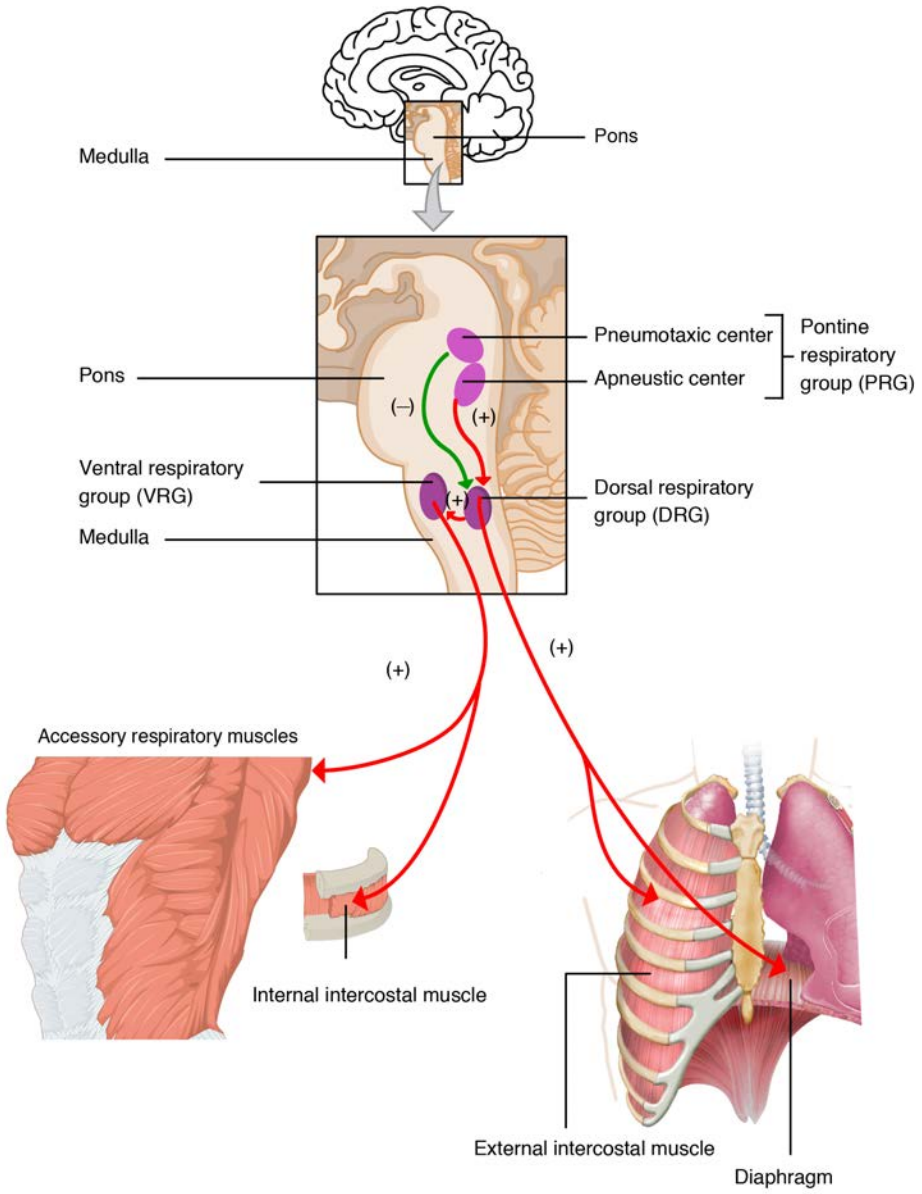



**Figure 22.20 Respiratory Centers of the Brain**

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, positive-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 $CO_2$ 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 $H^+$ 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 ($N_2$) | 78.6 | 597.4 |
| Oxygen ($O_2$) | 20.9 | 158.8 |
| Water ($H_2O$) | 0.04 | 3.0 |
| Carbon dioxide ($CO_2$) | 0.004 | 0.3 |
| Others | 0.0006 | 0.5 |
| Total composition/total atmospheric pressure | 100% | 760.0 |

Table 22.2

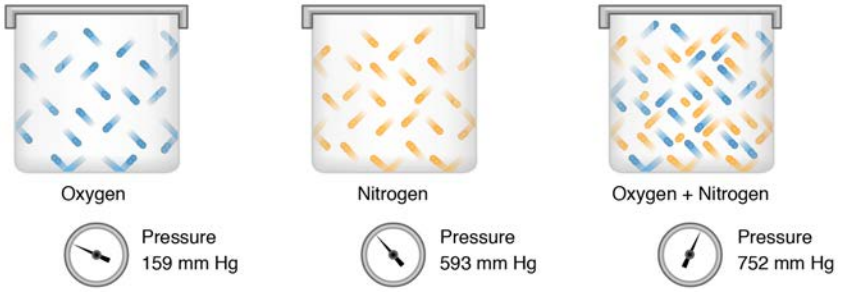



**Figure 22.21 Partial and Total Pressures of a Gas** Partial pressure is the force exerted by a gas. The sum of the partial pressures of all the gases in a mixture equals the total pressure.

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 ($N_2$) | 74.9 | 569 |
| Oxygen ($O_2$) | 13.7 | 104 |
| Water ($H_2O$) | 6.2 | 40 |
| Carbon dioxide ($CO_2$) | 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 the oxygenated pulmonary venous blood 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 serves 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.

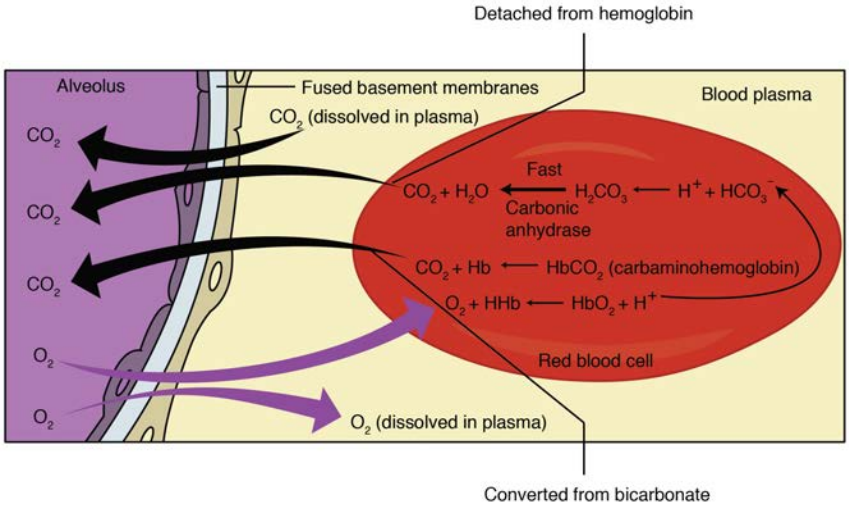



**Figure 22.22 External Respiration** In external respiration, oxygen diffuses across the respiratory membrane from the alveolus to the capillary, whereas carbon dioxide diffuses out of the capillary into the alveolus.

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.

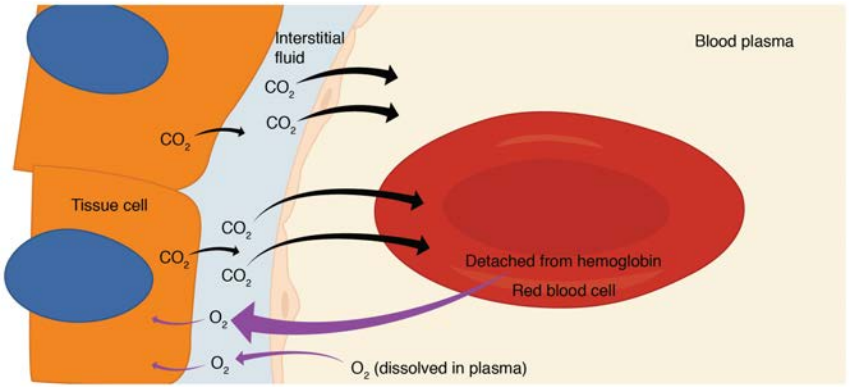



**Figure 22.23 Internal Respiration** Oxygen diffuses out of the capillary and into cells, whereas carbon dioxide diffuses out of cells and into the capillary.

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 erythrocyte contains four iron ions, and because of this, each erythrocyte 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** ($Hb–O_2$), 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.

$$Hb + O_2 \leftrightarrow Hb - O_2$$

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.

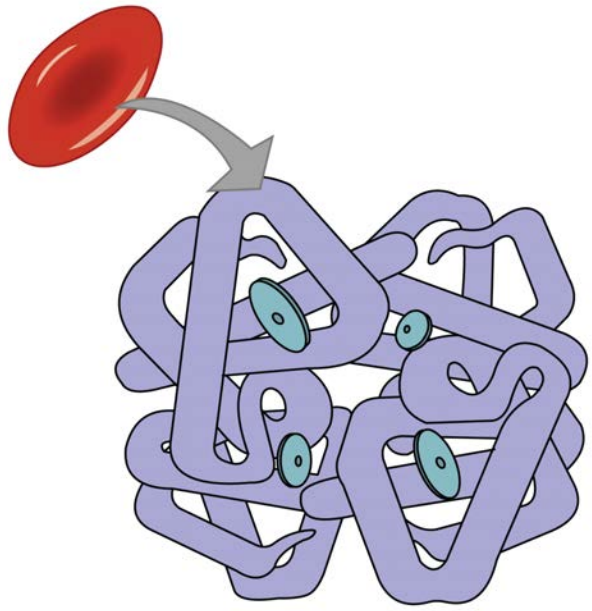


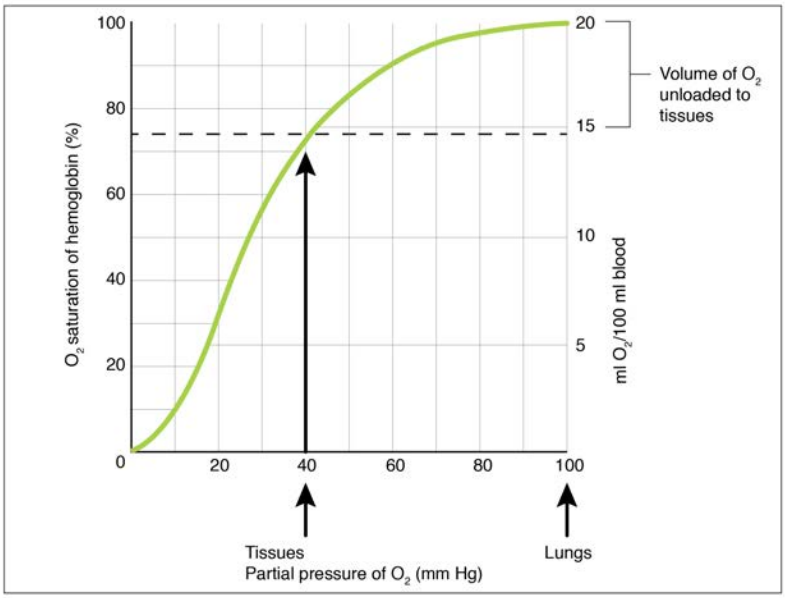
**Figure 22.25 Erythrocyte and Hemoglobin** Hemoglobin consists of four subunits, each of which contains one molecule of iron.

### 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.

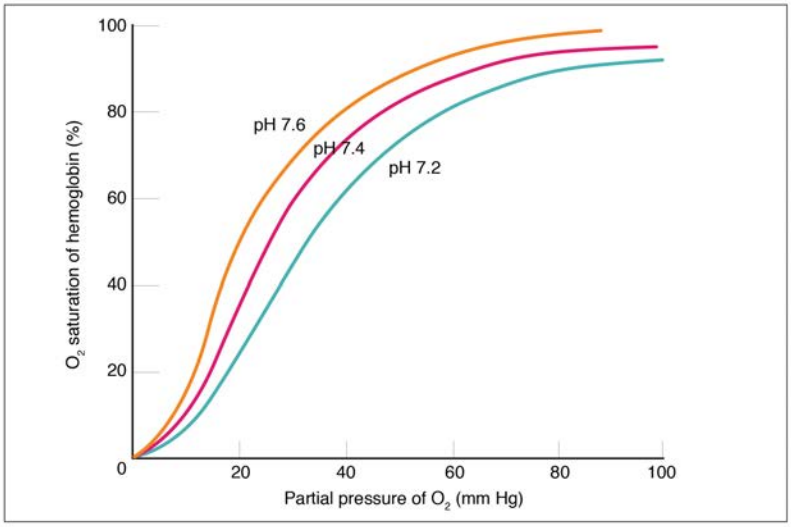
## Oxygen Dissociation from Hemoglobin

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.



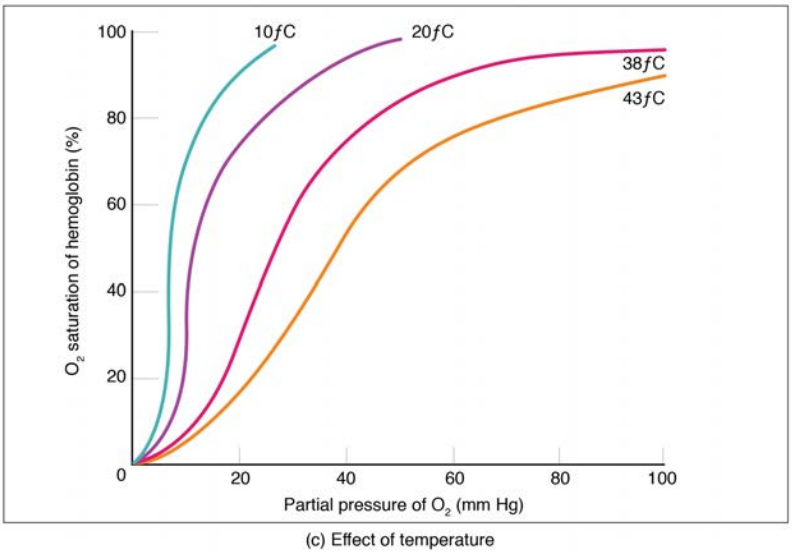

(a) Partial pressure of oxygen and hemoglobin saturation

**(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/disassociation 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.

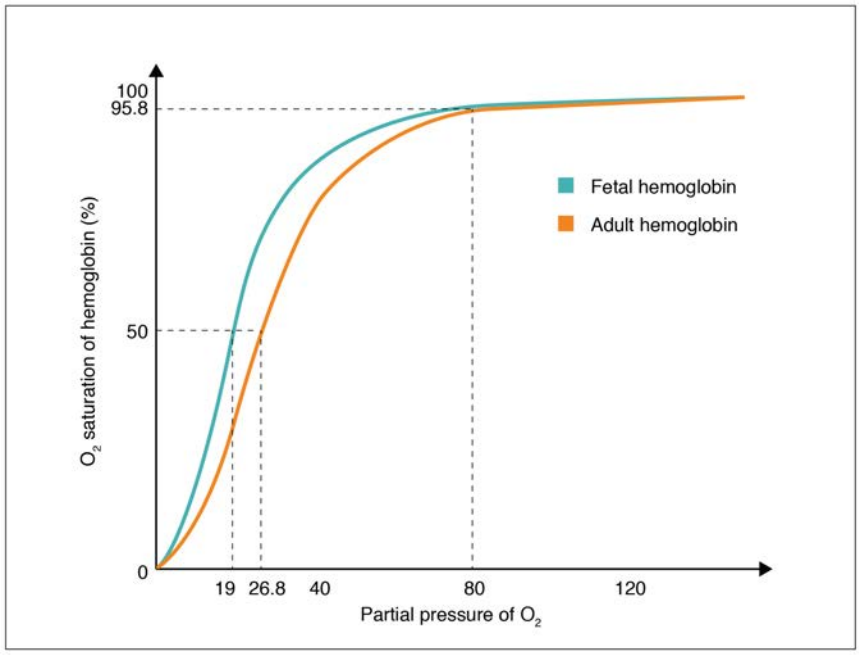



**Figure 22.27 Oxygen-Hemoglobin Dissociation Curves in Fetus and Adult** Fetal hemoglobin has a greater affinity for oxygen than does adult hemoglobin.

## 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 ($HCO_3^-$), which also dissolves in plasma. The third mechanism of carbon dioxide transport is similar to the transport of oxygen by erythrocytes (Figure 22.28).

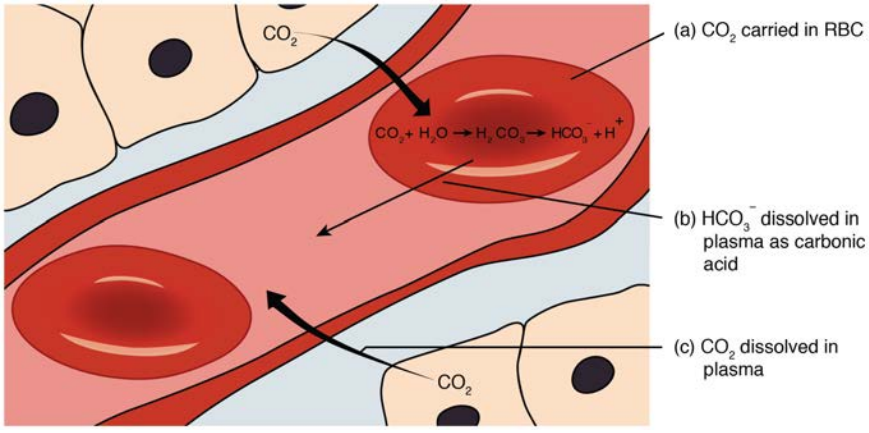



**Figure 22.28 Carbon Dioxide Transport** Carbon dioxide is transported by three different methods: (a) in erythrocytes; (b) after forming carbonic acid ($H_2CO_3$), which is dissolved in plasma; (c) and in plasma.

### 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 ($H_2CO_3$), which dissociates into two ions: bicarbonate ($HCO_3^-$) and hydrogen ($H^+$). The following formula depicts this reaction:

$$CO_2 + H_2O \overset{CA}{\leftrightarrow} H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

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 ($Cl^-$) 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:

$$CO_2 + Hb \leftrightarrow HbCO_2$$

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 |

Table 22.4

**Partial Pressure of Oxygen at Different Altitudes**

| Example location | Altitude (feet above sea level) | Atmospheric pressure (mm Hg) | Partial pressure of oxygen (mm Hg) |
|---|---|---|---|
| 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).

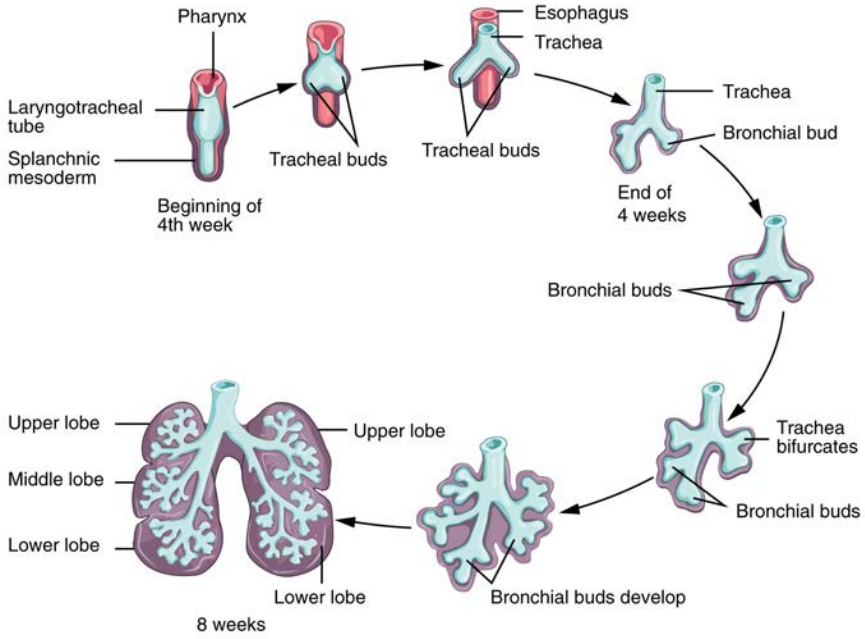



**Figure 22.29 Development of the Lower Respiratory System**

### 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.


### 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 ($HCO_3^-$) with chloride ($Cl^-$) 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 bud** median dome that forms from the endoderm of the foregut

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

**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** ($Hb–O_2$) 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

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

**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

**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 to 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)** 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)** 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)** 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?
- a. The diaphragm moves downward.
- b. The rib cage is compressed.
- c. The thoracic cavity volume decreases.
- d. The ribs and sternum move upward.

**19.** Which of the following prevents the alveoli from collapsing?
- a. residual volume
- b. tidal volume
- c. expiratory reserve volume
- d. inspiratory reserve volume

**20.** Gas moves from an area of _____ partial pressure to an area of _____ partial pressure.
- a. low; high
- b. low; low
- c. high; high
- d. high; low

**21.** When ventilation is not sufficient, which of the following occurs?
- a. The capillary constricts.
- b. The capillary dilates.
- c. The partial pressure of oxygen in the affected alveolus increases.
- d. The bronchioles dilate.

**22.** Gas exchange that occurs at the level of the tissues is called _____.
- a. external respiration
- b. interpulmonary respiration
- c. internal respiration
- d. 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?
- a. It diffuses into the blood.
- b. It diffuses into the alveoli.
- c. The gradient is too small for carbon dioxide to diffuse.
- d. It decomposes into carbon and oxygen.

**24.** Oxyhemoglobin forms by a chemical reaction between which of the following?
- a. hemoglobin and carbon dioxide
- b. carbonic anhydrase and carbon dioxide
- c. hemoglobin and oxygen
- d. carbonic anhydrase and oxygen

**25.** Which of the following factors play a role in the oxygen–hemoglobin saturation/dissociation curve?
- a. temperature
- b. pH
- c. BPG
- d. all of the above

**26.** Which of the following occurs during the chloride shift?
- a. Chloride is removed from the erythrocyte.
- b. Chloride is exchanged for bicarbonate.
- c. Bicarbonate is removed from the erythrocyte.
- d. 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 _____.
- a. Haldane effect
- b. Bohr effect
- c. Dalton’s law
- d. Henry’s law

**28.** Increased ventilation that results in an increase in blood pH is called _____.
- a. hyperventilation

b. hyperpnea
c. acclimatization
d. apnea

**29.** Exercise can trigger symptoms of AMS due to which of the following?
a. low partial pressure of oxygen
b. low atmospheric pressure
c. abnormal neural signals
d. small venous reserve of oxygen

**30.** Which of the following stimulates the production of erythrocytes?
a. AMS
b. high blood levels of carbon dioxide
c. low atmospheric pressure
d. erythropoietin

**31.** The olfactory pits form from which of the following?
a. mesoderm
b. cartilage
c. ectoderm
d. endoderm

**32.** A full complement of mature alveoli are present by _____.
a. early childhood, around 8 years of age
b. birth
c. 37 weeks
d. 16 weeks

**33.** If a baby is born prematurely before type II cells produce sufficient pulmonary surfactant, which of the following might you expect?
a. difficulty expressing fluid
b. difficulty inflating the lungs
c. difficulty with pulmonary capillary flow
d. no difficulty as type I cells can provide enough surfactant for normal breathing

**34.** When do fetal breathing movements begin?
a. around week 20
b. around week 37
c. around week 16
d. after birth

**35.** What happens to the fluid that remains in the lungs after birth?
a. It reduces the surface tension of the alveoli.
b. It is expelled shortly after birth.
c. It is absorbed shortly after birth.
d. 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**).

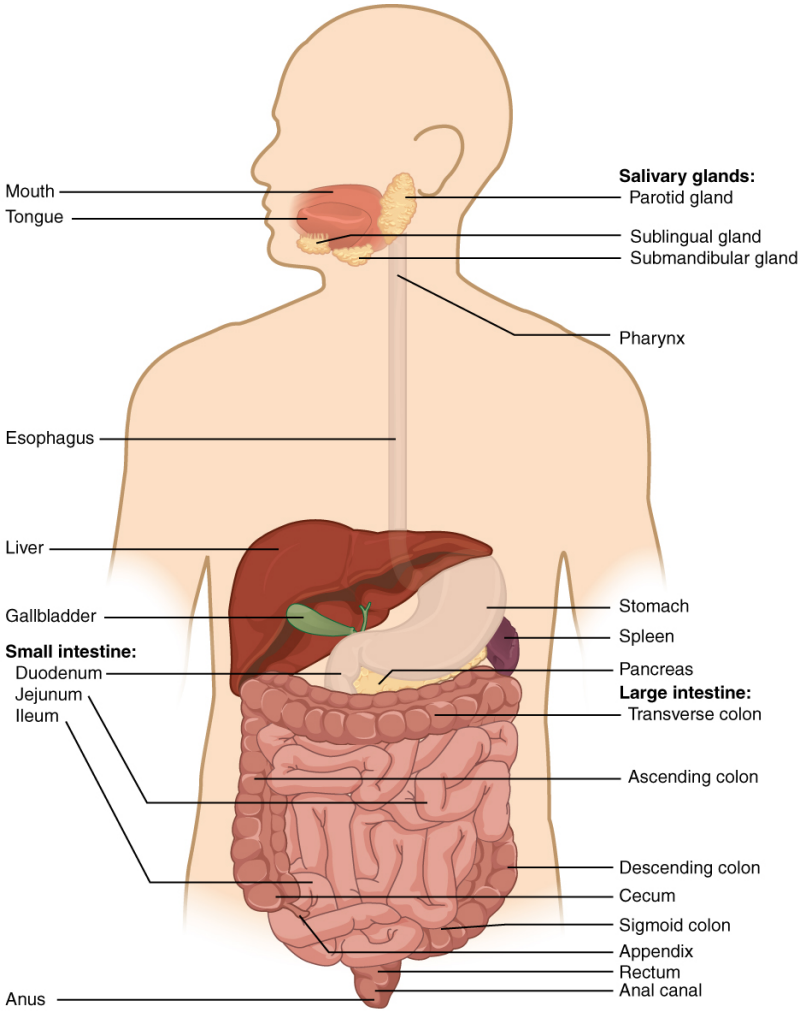



**Figure 23.2 Components of the Digestive System** All digestive organs play integral roles in the life-sustaining process of digestion.

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 |
| 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**).

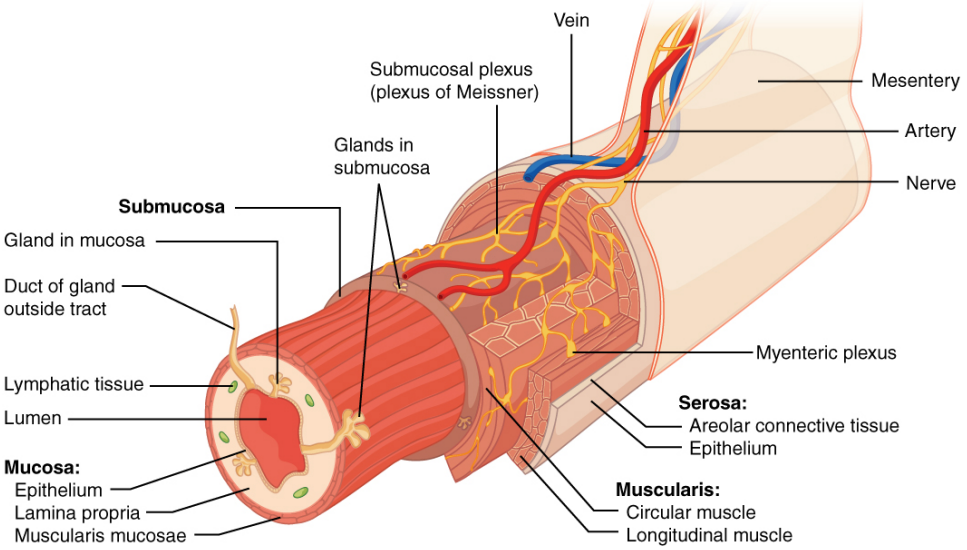



**Figure 23.3 Layers of the Alimentary Canal** The wall of the alimentary canal has four basic tissue layers: the mucosa, submucosa, muscularis, and serosa.

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 **muscalaris** (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.

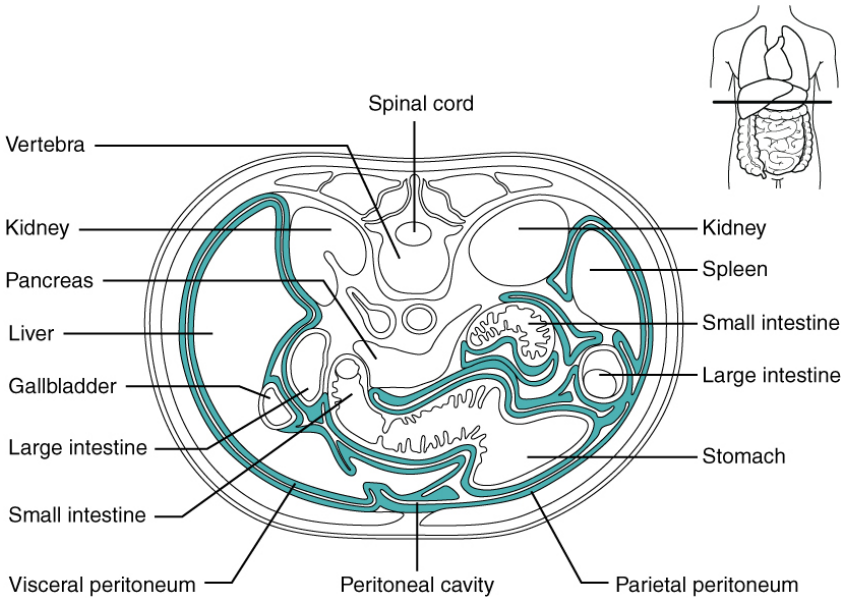



**Figure 23.4 The Peritoneum** A cross-section of the abdomen shows the relationship between abdominal organs and the peritoneum (darker lines).

## 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 |
| Falciform ligament | Anchors the liver to the anterior abdominal wall and inferior border of the diaphragm |

**Table 23.2**

**The Five Major Peritoneal Folds**

| Fold | Description |
|---|---|
| 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)** 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)** 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 | Ingests food<br>Chews and mixes food<br>Begins chemical breakdown of carbohydrates<br>Moves food into the pharynx<br>Begins breakdown of lipids via lingual lipase | Moistens and dissolves food, allowing you to taste it<br>Cleans and lubricates the teeth and oral cavity<br>Has some antimicrobial activity |
| Pharynx | Propels food from the oral cavity to the esophagus | Lubricates food and passageways |
| Esophagus | Propels food to the stomach | Lubricates food and passageways |
| Stomach | Mixes and churns food with gastric juices to form chyme<br>Begins chemical breakdown of proteins<br>Releases food into the duodenum as chyme<br>Absorbs some fat-soluble substances (for example, alcohol, aspirin)<br>Possesses antimicrobial functions | Stimulates protein-digesting enzymes<br>Secretes intrinsic factor required for vitamin $B_{12}$ absorption in small intestine |
| Small intestine | Mixes chyme with digestive juices<br>Propels food at a rate slow enough for digestion and absorption<br>Absorbs breakdown products of carbohydrates, proteins, lipids, and nucleic acids, along with vitamins, minerals, and water<br>Performs physical digestion via segmentation | Provides optimal medium for enzymatic activity |
| Accessory organs | Liver: produces bile salts, which emulsify lipids, aiding their digestion and absorption<br>Gallbladder: stores, concentrates, and releases bile<br>Pancreas: produces digestive enzymes and bicarbonate | Bicarbonate-rich pancreatic juices help neutralize acidic chyme and provide optimal environment for enzymatic activity |
| Large intestine | Further breaks down food residues<br>Absorbs most residual water, electrolytes, and vitamins produced by enteric bacteria<br>Propels feces toward rectum<br>Eliminates feces | Food residue is concentrated and temporarily stored prior to defecation<br>Mucus eases passage of feces through colon |

**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.

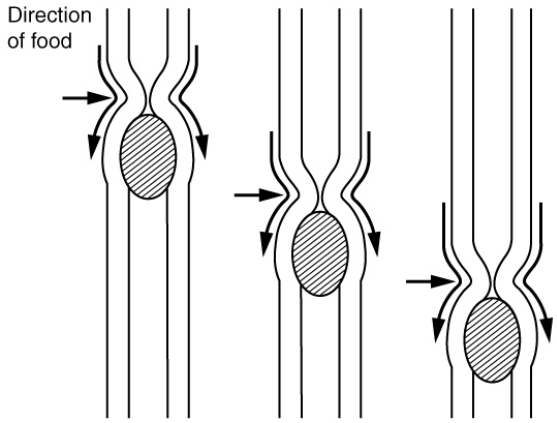



**Figure 23.5 Peristalsis** Peristalsis moves food through the digestive tract with alternating waves of muscle contraction and relaxation.

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.

Aging 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**).

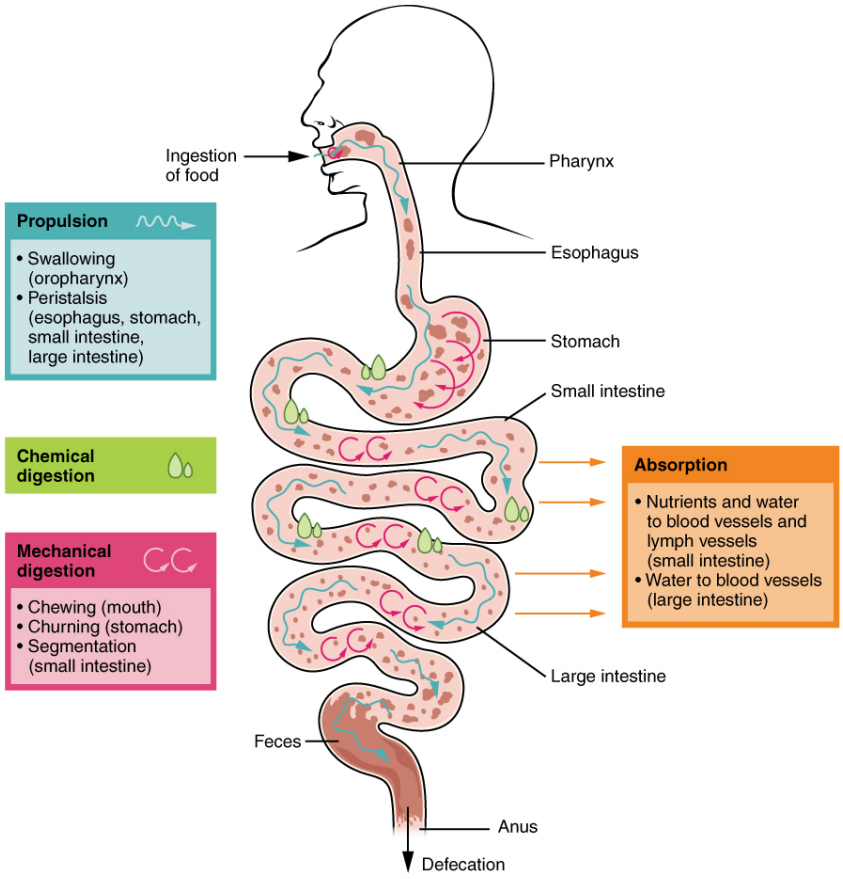



**Figure 23.6 Digestive Processes** The digestive processes are ingestion, propulsion, mechanical digestion, chemical digestion, absorption, and defecation.

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**).

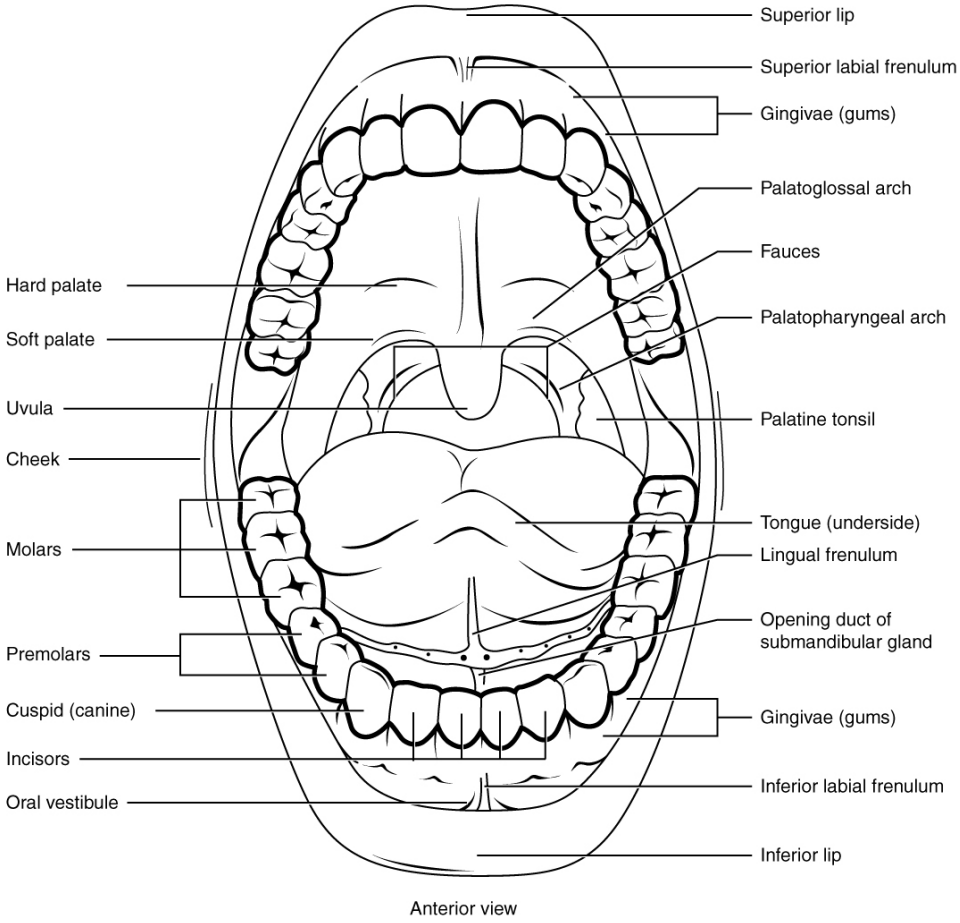



**Figure 23.7 Mouth** The mouth includes the lips, tongue, palate, gums, and teeth.

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.

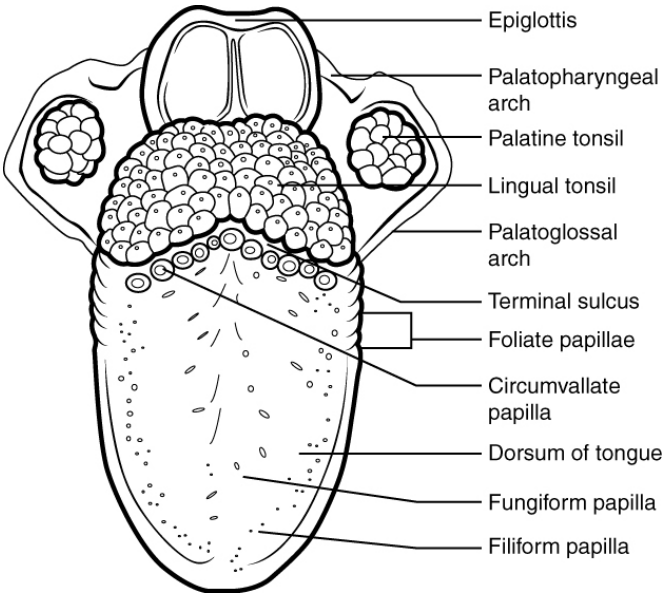



**Figure 23.8 Tongue** This superior view of the tongue shows the locations and types of lingual papillae.

## 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 salvia 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.

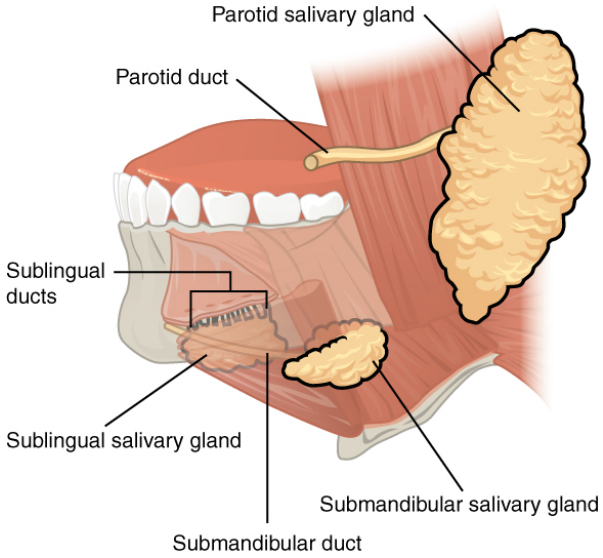



**Figure 23.9 Salivary glands** The major salivary glands are located outside the oral mucosa and deliver saliva into the mouth through ducts.

## 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 **cuspids** (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 cuspids are the eight **premolars** (or bicuspids), 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.

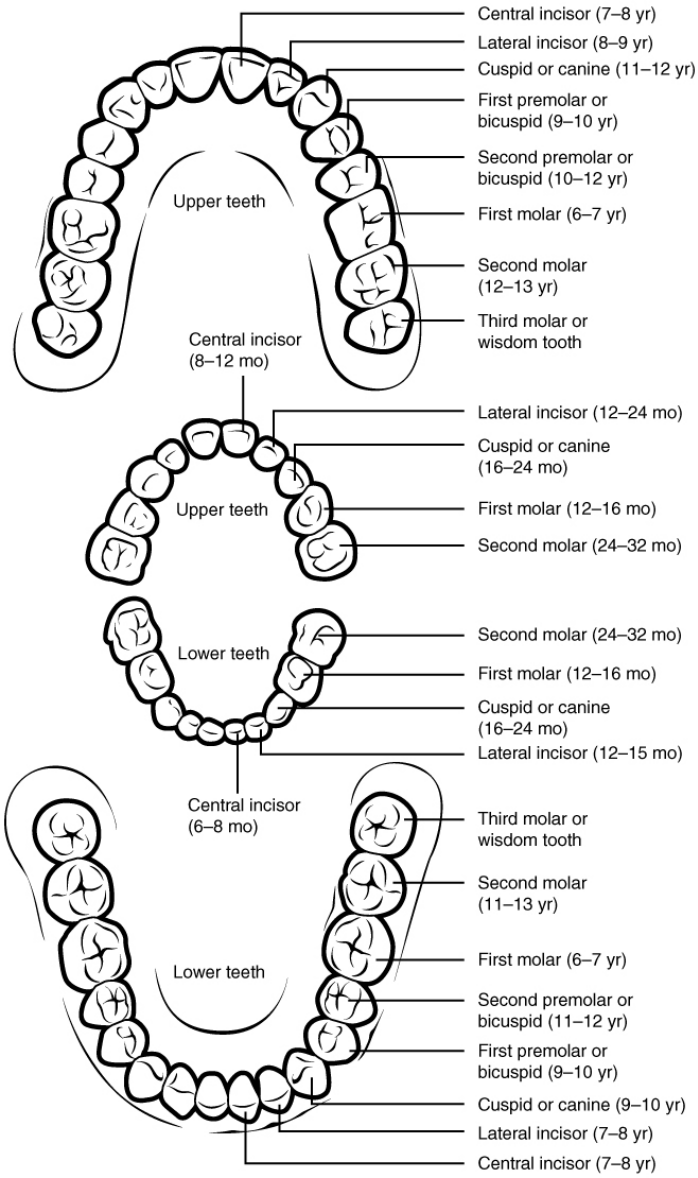



**Figure 23.10 Permanent and Deciduous Teeth** This figure of two human dentitions shows the arrangement of teeth in the maxilla and mandible, and the relationship between the deciduous and permanent teeth.

## 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.

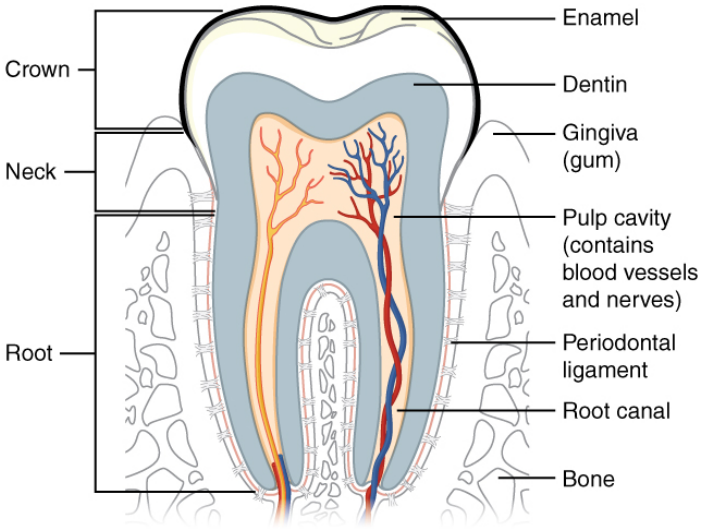



**Figure 23.11 The Structure of the Tooth** This longitudinal section through a molar in its alveolar socket shows the relationships between enamel, dentin, and pulp.

### 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<br>Moisten, soften, and dissolve food<br>Clean the mouth and teeth<br>Salivary amylase breaks down starch |
| Tongue's extrinsic muscles | Move tongue sideways, and in and out | Manipulate food for chewing<br>Shape food into a bolus<br>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 |

**Table 23.4**

### Digestive Functions of the Mouth

| Structure | Action | Outcome |
|---|---|---|
| Lingual glands | Secrete lingual lipase | Activated in the stomach<br>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.

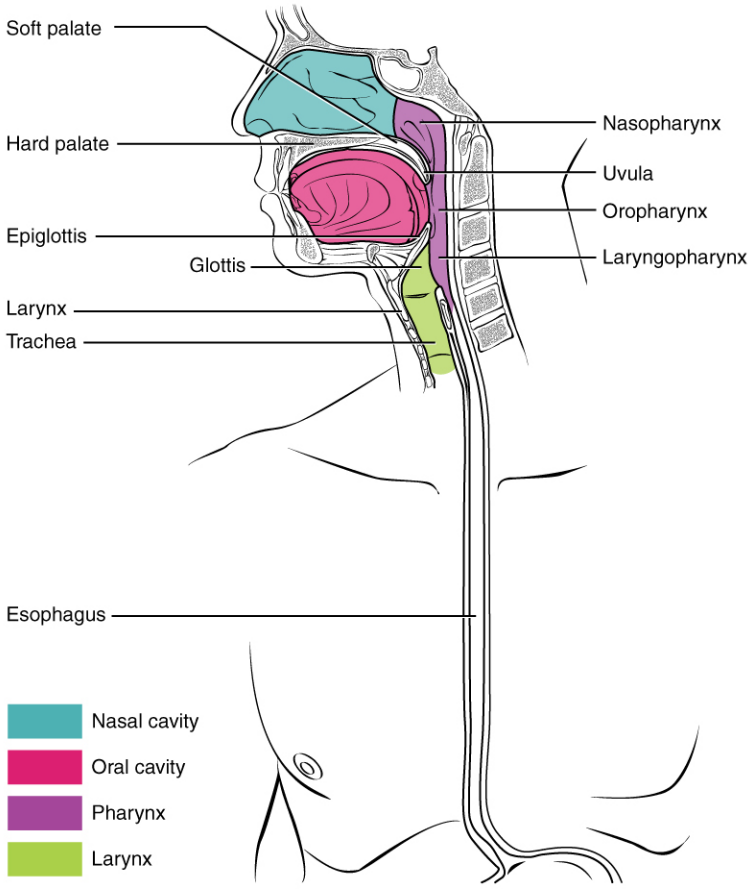



**Figure 23.12 Pharynx** The pharynx runs from the nostrils to the esophagus and the larynx.

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).

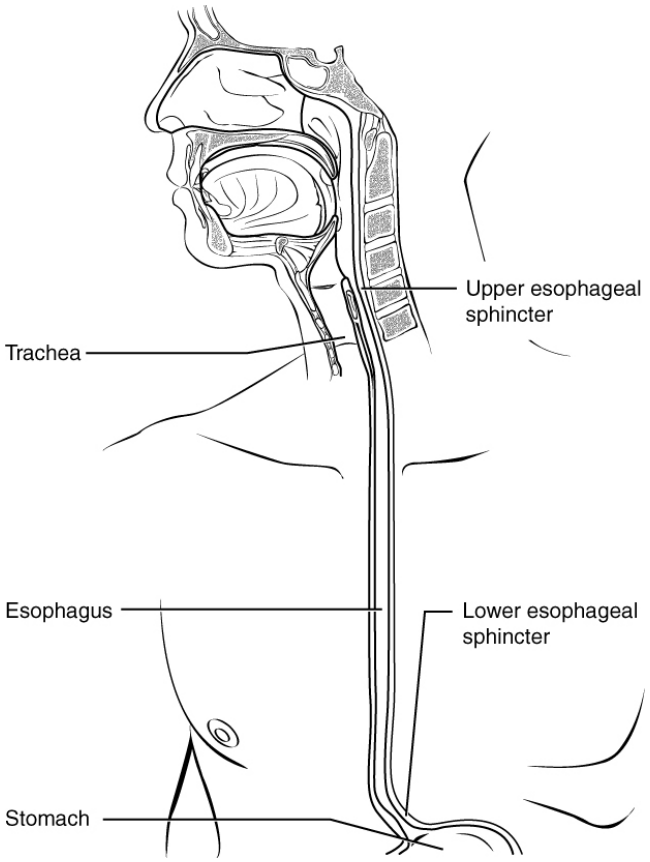



**Figure 23.13 Esophagus** The upper esophageal sphincter controls the movement of food from the pharynx to the esophagus. The lower esophageal sphincter controls the movement of food from the esophagus to the stomach.

### 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.

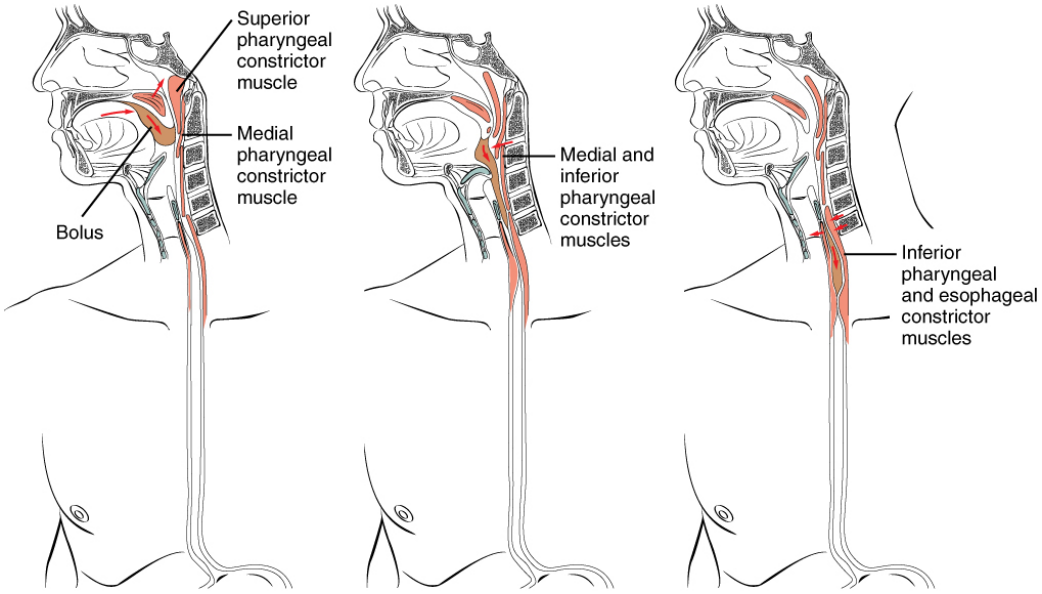



**Figure 23.14 Deglutition** Deglutition includes the voluntary phase and two involuntary phases: the pharyngeal phase and the esophageal phase.

### 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.

**Interactive LINK**

Watch this **animation (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**.

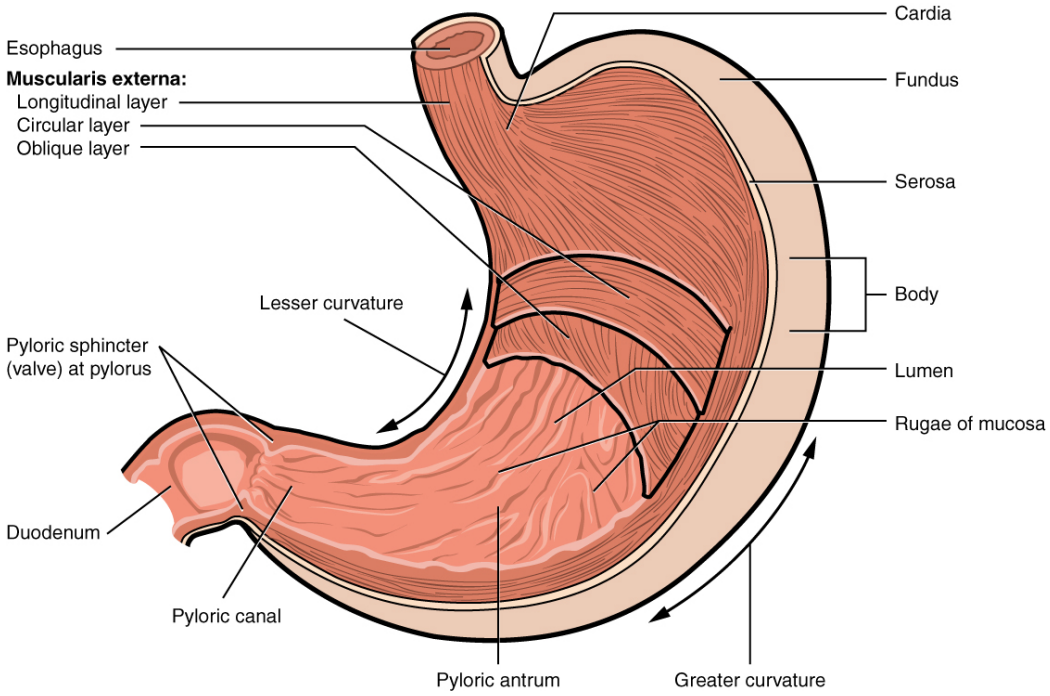



**Figure 23.15 Stomach** The stomach has four major regions: the cardia, fundus, body, and pylorus. The addition of an inner oblique smooth muscle layer gives the muscularis the ability to vigorously churn and mix food.

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.

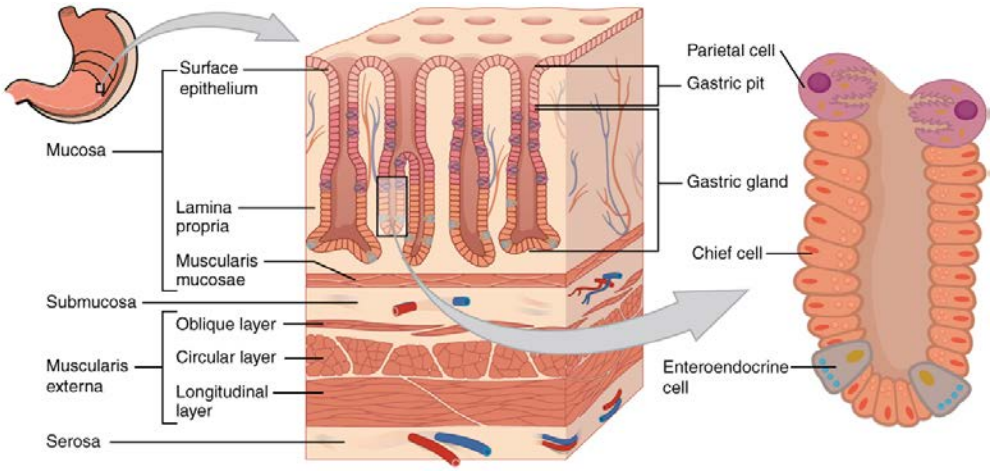



**Figure 23.16 Histology of the Stomach** The stomach wall is adapted for the functions of the stomach. In the epithelium, gastric pits lead to gastric glands that secrete gastric juice. The gastric glands (one gland is shown enlarged on the right) contain different types of cells that secrete a variety 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 $B_{12}$ 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 |

Table 23.6

**Hormones Secreted by the Stomach**

| Hormone | Production site | Production stimulus | Target organ | Action |
|---|---|---|---|---|
| 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.

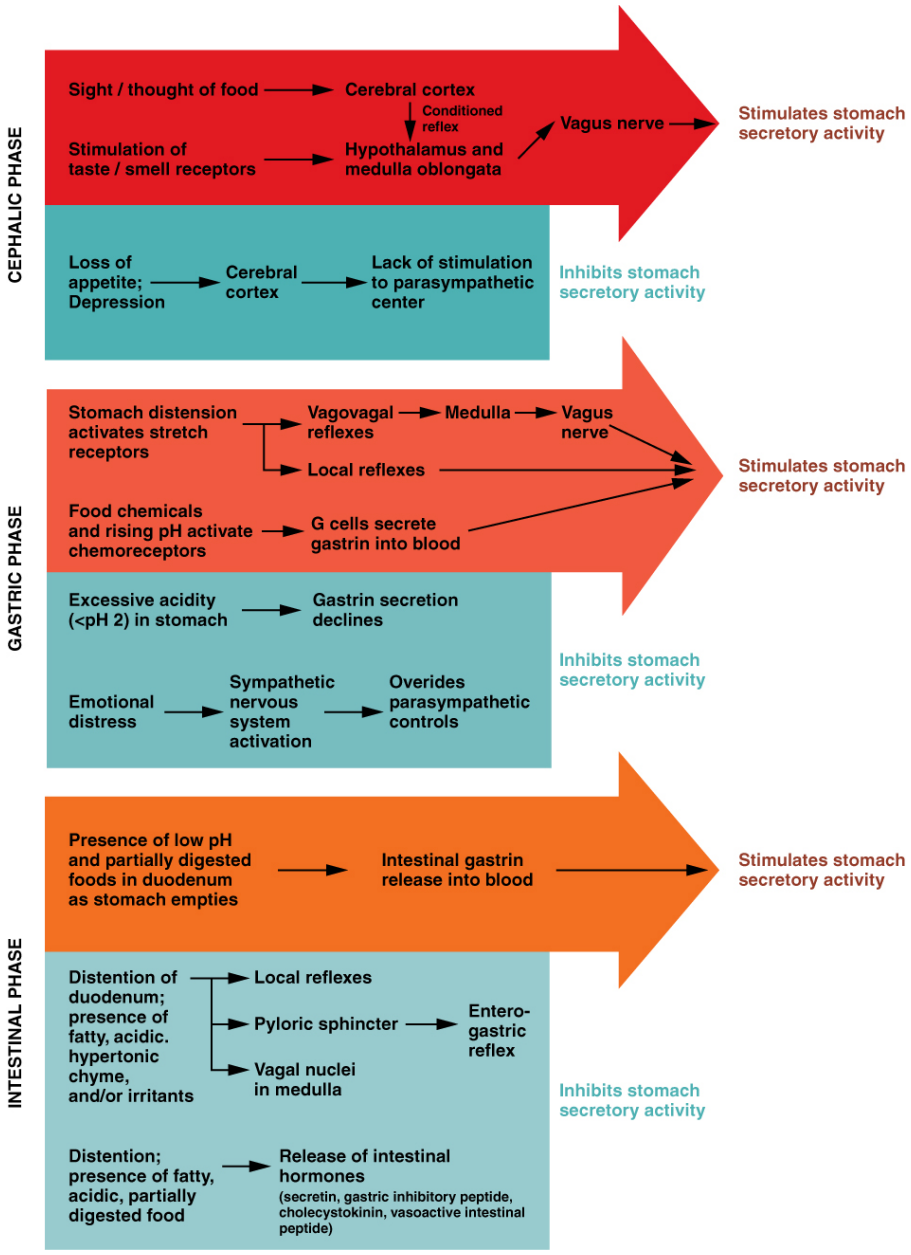



**Figure 23.17 The Three Phases of Gastric Secretion** Gastric secretion occurs in three phases: cephalic, gastric, and intestinal. During each phase, the secretion of gastric juice can be stimulated or inhibited.

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 after 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 $B_{12}$, 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 $B_{12}$ 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 $m^2$, 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.

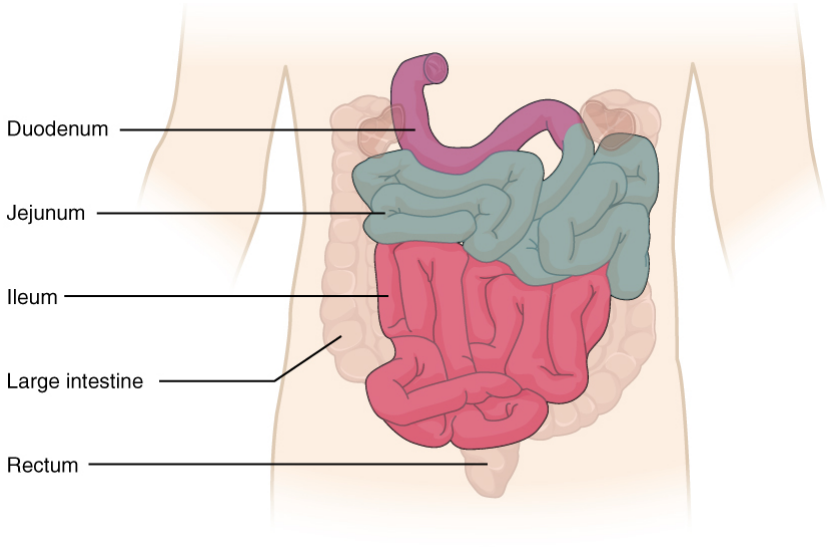



**Figure 23.18 Small Intestine** The three regions of the small intestine are the duodenum, jejunum, and ileum.

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.

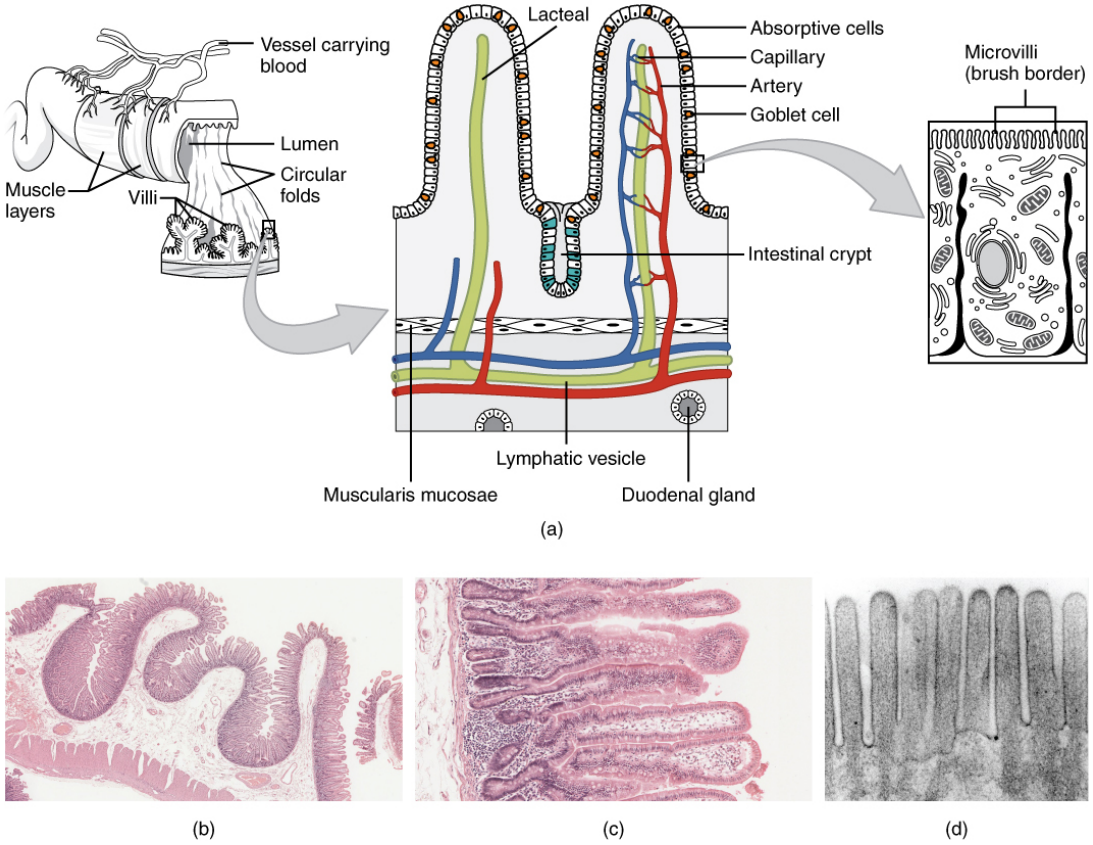



**Figure 23.19 Histology of the Small Intestine** (a) The absorptive surface of the small intestine is vastly enlarged by the presence of circular folds, villi, and microvilli. (b) Micrograph of the circular folds. (c) Micrograph of the villi. (d) Electron micrograph of the microvilli. From left to right, 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 circulare, 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 $\mu$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)** 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**).

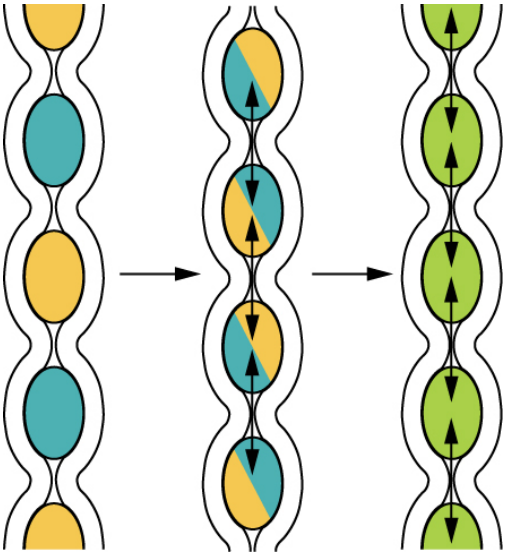


**Figure 23.20 Segmentation** Segmentation separates chyme and then pushes it back together, mixing it and providing time for digestion and absorption.

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.

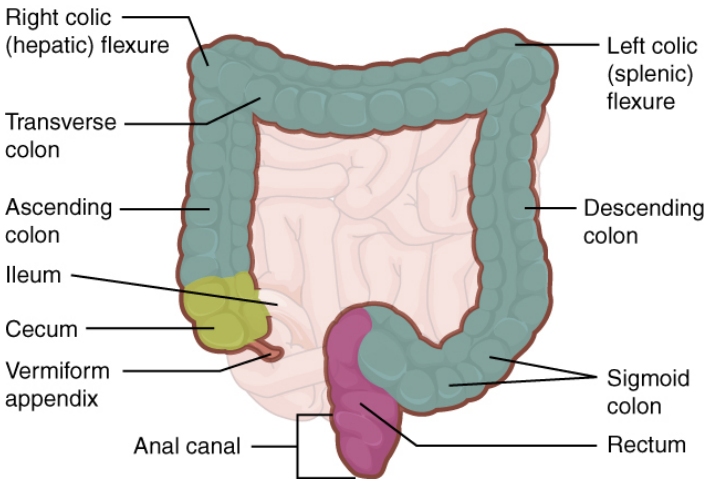



**Figure 23.21 Large Intestine** The large intestine includes the cecum, colon, and rectum.

## 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.

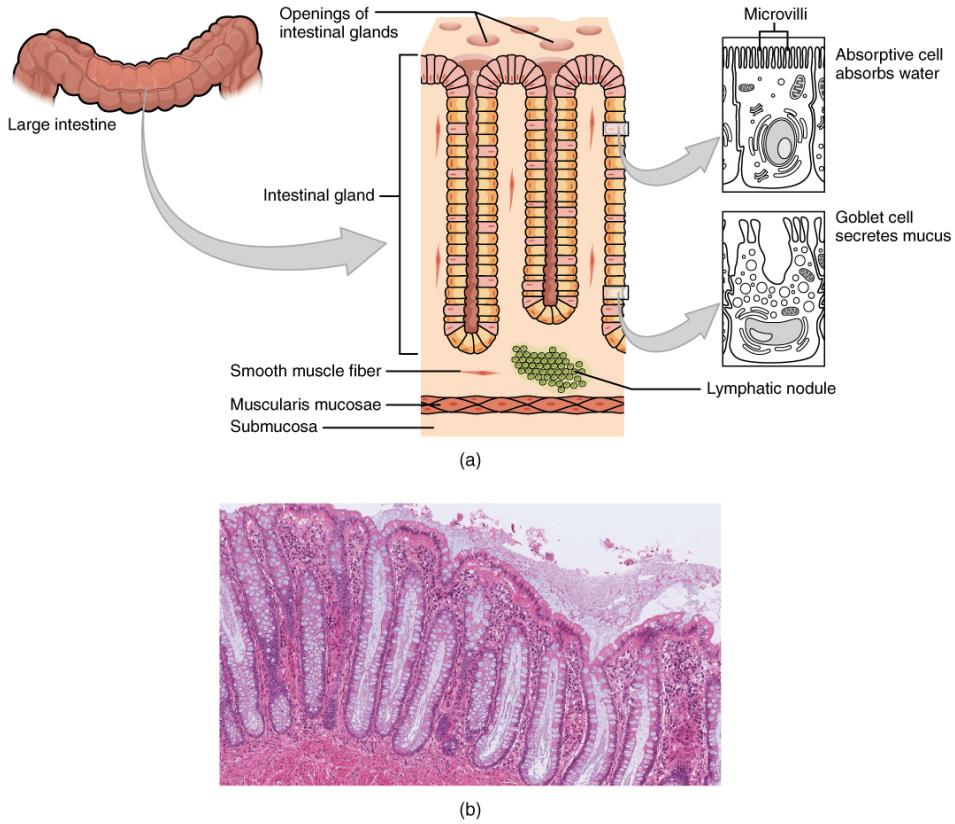



**Figure 23.22 Histology of the large Intestine** (a) The histologies of the large intestine and small intestine (not shown) are adapted for the digestive functions of each organ. (b) This micrograph shows the colon's simple columnar epithelium and goblet cells. LM x 464. (credit b: Micrograph provided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

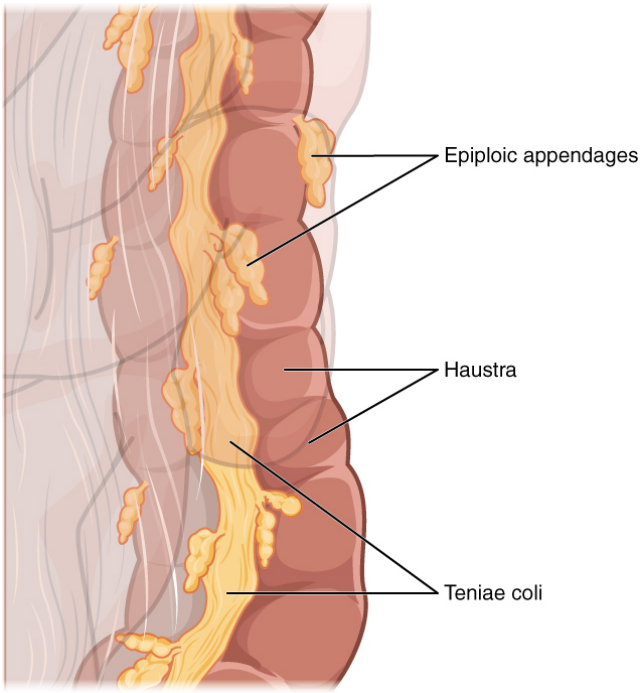



**Figure 23.23 Teniae Coli, Haustra, and Epiploic Appendages**

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.

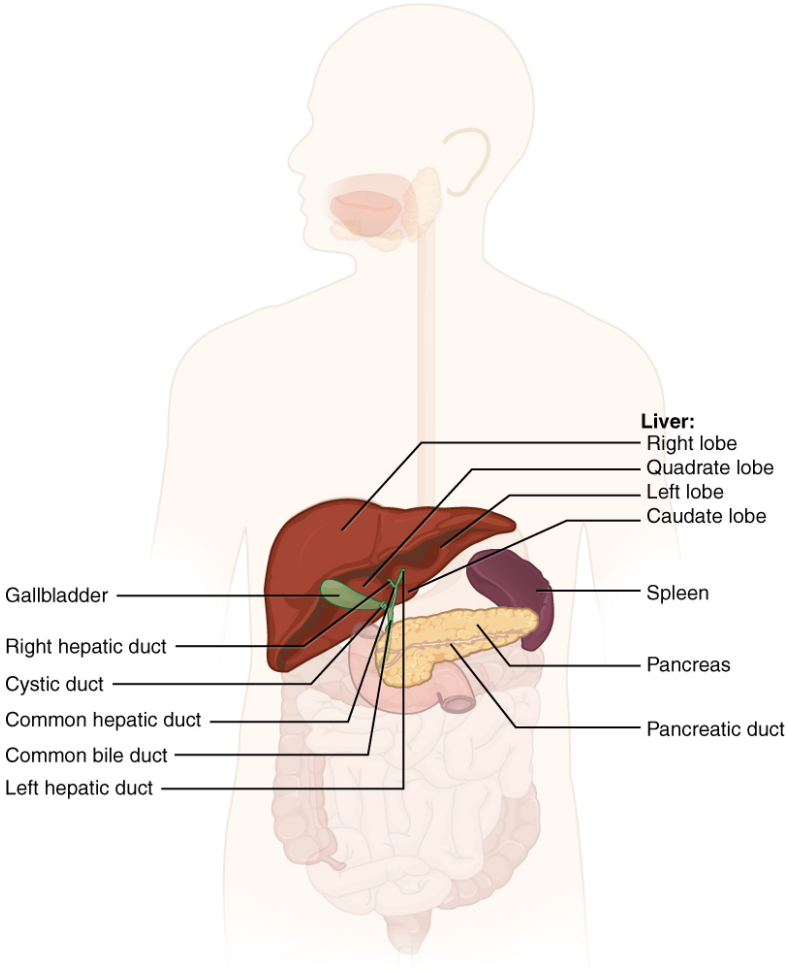



**Figure 23.24 Accessory Organs** The liver, pancreas, and gallbladder are considered accessory digestive organs, but their roles in the digestive system are vital.

## 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.

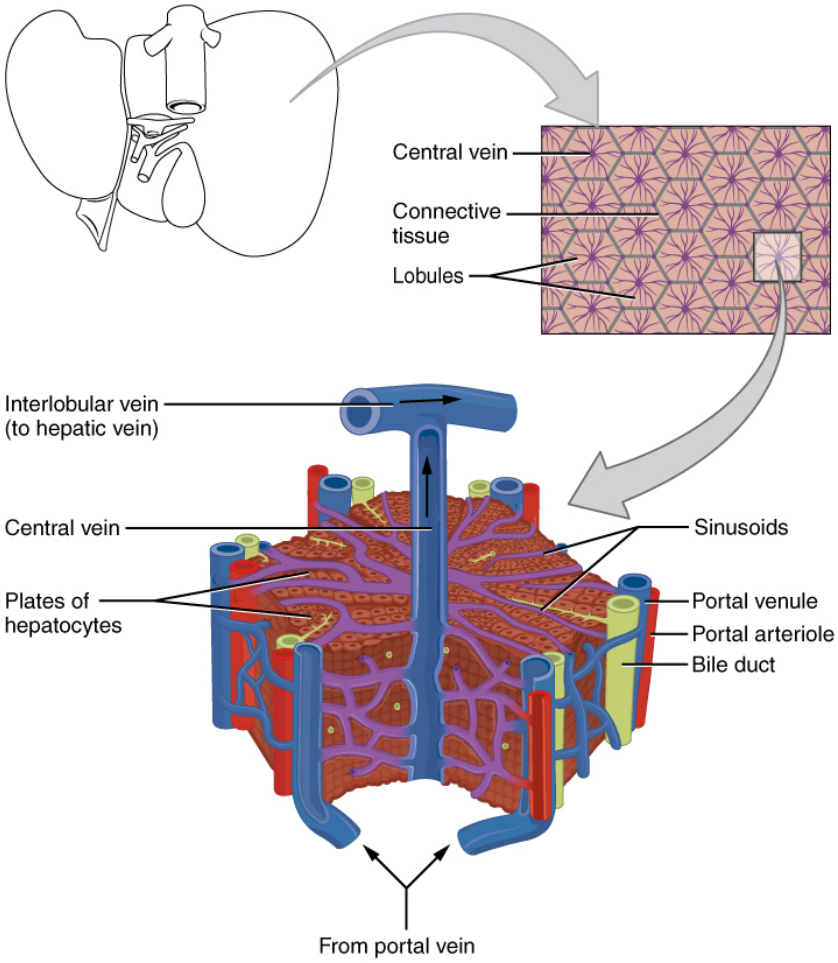



**Figure 23.25 Microscopic Anatomy of the Liver** The liver receives oxygenated blood from the hepatic artery and nutrient-rich deoxygenated blood from the hepatic portal vein.

## 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 $\mu$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.

**Interactive LINK**


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**).

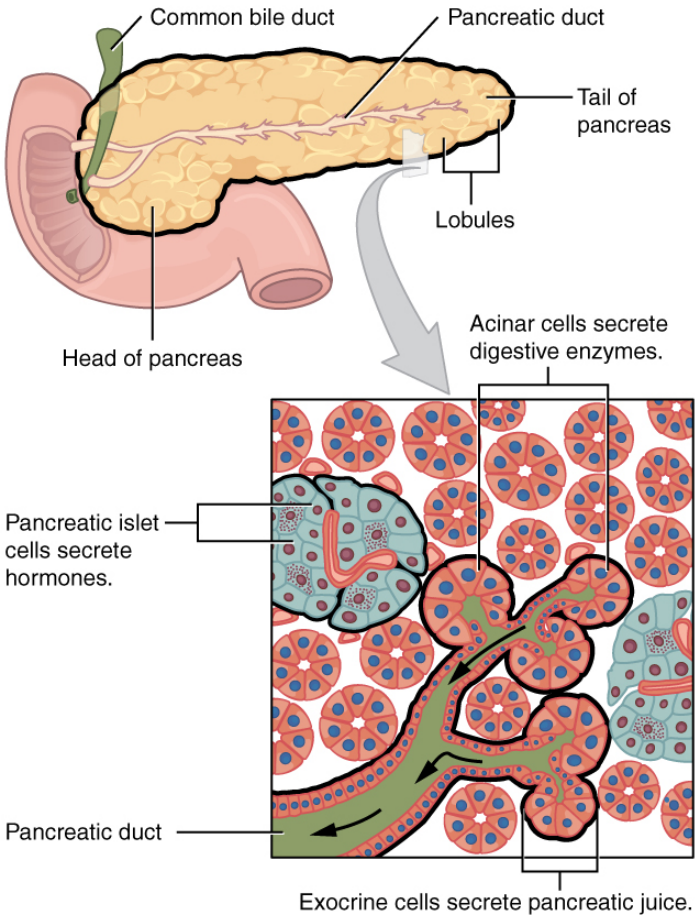



**Figure 23.26 Exocrine and Endocrine Pancreas** The pancreas has a head, a body, and a tail. It delivers pancreatic juice to the duodenum through the pancreatic duct.

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 nested 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.

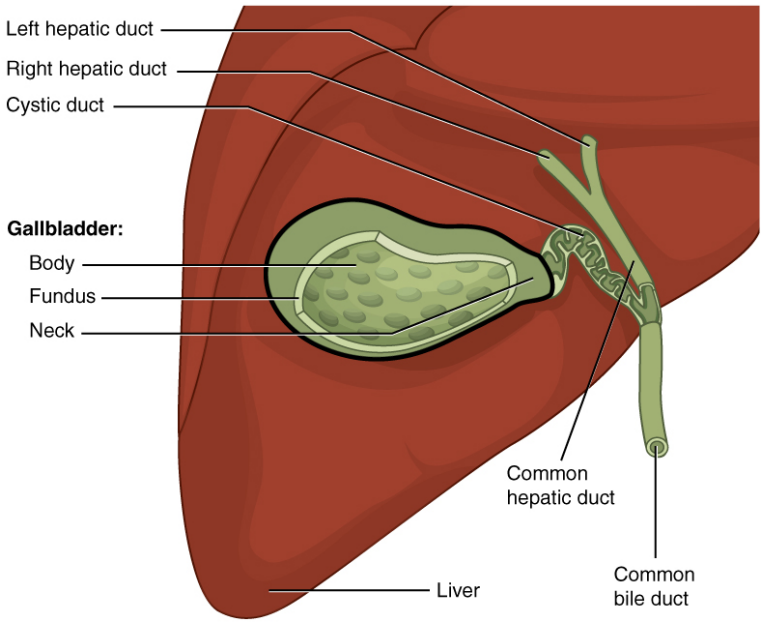



**Figure 23.27 Gallbladder** The gallbladder stores and concentrates bile, and releases it into the two-way cystic duct when it is needed by the small intestine.

# 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.

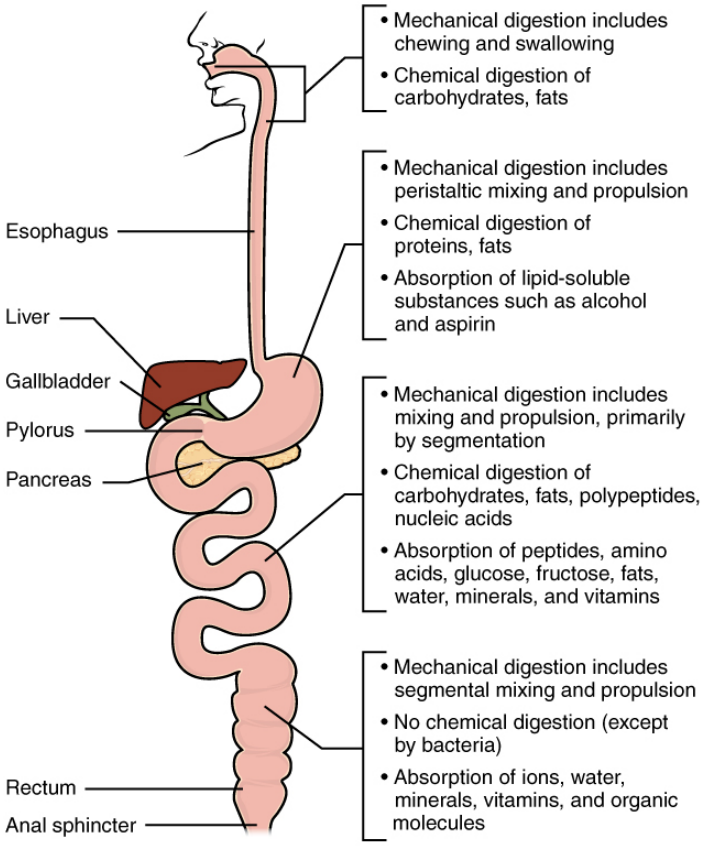



**Figure 23.28 Digestion and Absorption** Digestion begins in the mouth and continues as food travels through the small intestine. Most absorption occurs in the small intestine.

## 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 | α-Dextrinase | Small intestine | α-Dextrins | Glucose |
| Brush border enzymes | Enteropeptidase | Small intestine | Trypsinogen | Trypsin |

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

## The Digestive Enzymes

| Enzyme Category | Enzyme Name | Source | Substrate | Product |
|---|---|---|---|---|
| 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<br>Dipeptidase: dipeptides | Aminopeptidase: amino acids and peptides<br>Dipeptidase: amino acids |
| Brush border enzymes | Sucrase | Small intestine | Sucrose | Glucose and fructose |
| Pancreatic enzymes | Carboxy-peptidase* | 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<br>Deoxyribonuclease: deoxyribonucleic acids | Nucleotides |
| Pancreatic enzymes | Pancreatic amylase | Pancreatic acinar cells | Polysaccharides (starches) | α-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 **α-dextrinase** starts working on **α-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.

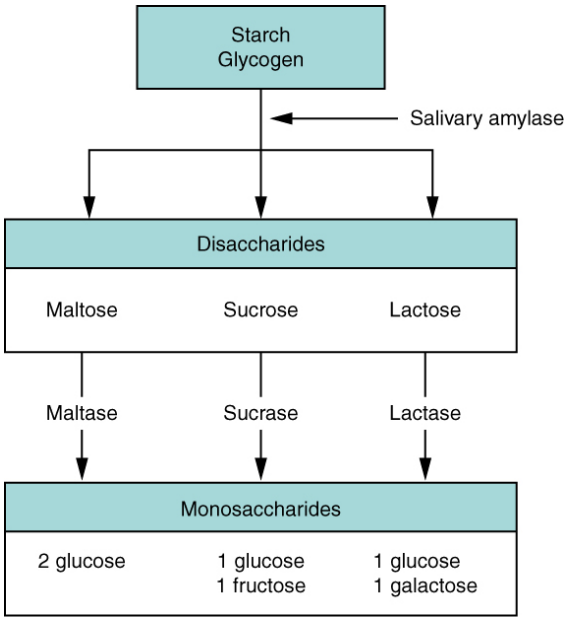



**Figure 23.29 Carbohydrate Digestion Flow Chart** Carbohydrates are broken down into their monomers in a series of steps.

## 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**).

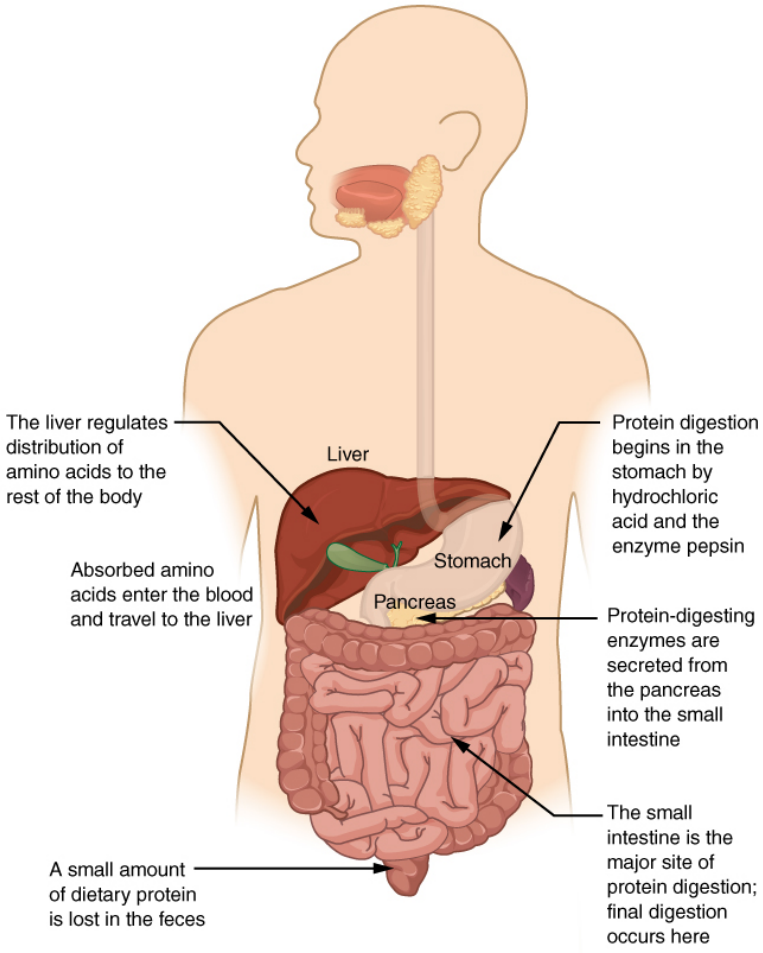



**Figure 23.30 Digestion of Protein** The digestion of protein begins in the stomach and is completed in the small intestine.

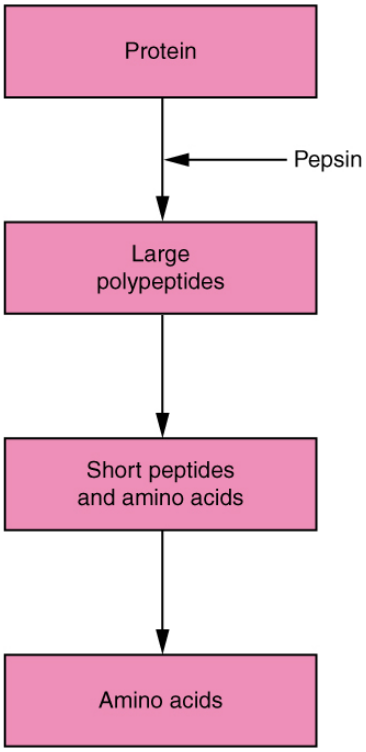



**Figure 23.31 Digestion of Protein Flow Chart** Proteins are successively broken down into their amino acid components.

### 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 $B_{12}$ 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**).

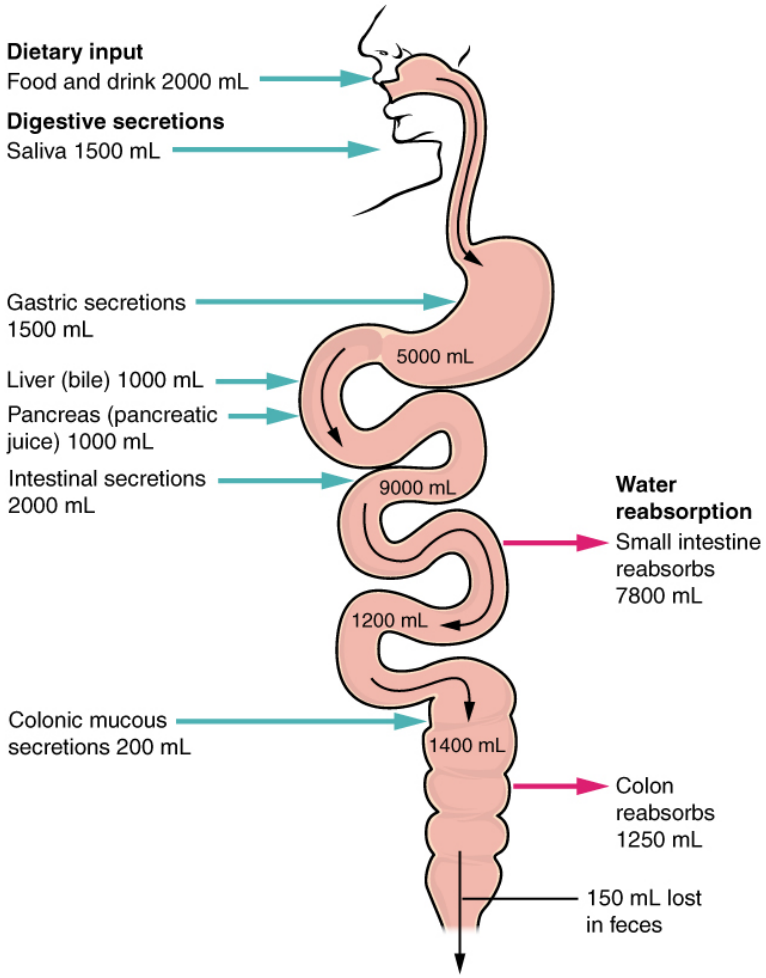



**Figure 23.32 Digestive Secretions and Absorption of Water** Absorption is a complex process, in which nutrients from digested food are harvested.

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 |
| Lipids | 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. Despite being hydrophobic, 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.

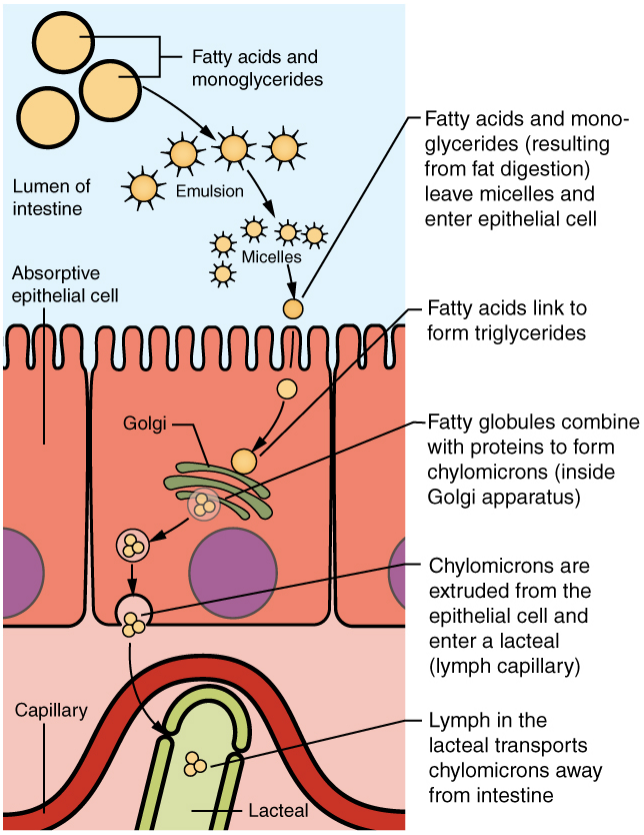



**Figure 23.33 Lipid Absorption** Unlike amino acids and simple sugars, lipids are transformed as they are absorbed through epithelial cells.

## 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-port 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 $B_{12}$, which is a very large molecule. Intrinsic factor secreted in the stomach binds to vitamin $B_{12}$, 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 canaliculus** small duct between hepatocytes that collects bile

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

**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 circulare) 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 proteins

**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 $B_{12}$ 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

**mucosal barrier** protective barrier that prevents gastric juice from destroying the stomach itself

**mucosa** innermost lining of the alimentary canal

**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

**ruga** fold of alimentary canal mucosa and submucosa in the empty stomach and other organs

**saccharolytic fermentation** anaerobic decomposition of carbohydrates

**salivary amylase** digestive enzyme in saliva that acts on starch

**salivary gland** an exocrine gland that secretes a digestive fluid called saliva

**saliva** aqueous solution of proteins and ions secreted into the mouth by the salivary glands

**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

**submucosal plexus** (plexus of Meissner) nerve supply that regulates activity of glands and smooth muscle

**submucosa** layer of dense connective tissue in the alimentary canal wall that binds the overlying mucosa to the underlying muscularis

**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

**α-dextrinase** brush border enzyme that acts on α-dextrins

**α-dextrin** breakdown product of starch

## 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 absorbs 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

**1.** By clicking on this **link (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?

**2.** Visit this **site (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.

**3.** Watch this **animation (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?

**4.** 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?

**5.** Watch this **animation (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?

**6.** 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?

**7.** 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?

## REVIEW QUESTIONS

**8.** Which of these organs is not considered an accessory digestive structure?
a. mouth
b. salivary glands
c. pancreas
d. liver

**9.** Which of the following organs is supported by a layer of adventitia rather than serosa?
a. esophagus
b. stomach
c. small intestine
d. large intestine

**10.** Which of the following membranes covers the stomach?
a. falciform ligament
b. mesocolon
c. parietal peritoneum
d. visceral peritoneum

**11.** Which of these processes occurs in the mouth?
a. ingestion
b. mechanical digestion
c. chemical digestion
d. all of the above

**12.** Which of these processes occurs throughout most of the alimentary canal?
a. ingestion
b. propulsion
c. segmentation
d. absorption

**13.** Which of the following stimuli activates sensors in the walls of digestive organs?
a. breakdown products of digestion
b. distension
c. pH of chyme
d. all of the above

**14.** Which of these statements about reflexes in the GI tract is false?
a. Short reflexes are provoked by nerves near the GI tract.
b. Short reflexes are mediated by the enteric nervous system.
c. Food that distends the stomach initiates long reflexes.
d. 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?
a. mucus
b. phosphate ions
c. chloride ions
d. urea

**16.** Which of these statements about the pharynx is true?
a. It extends from the nasal and oral cavities superiorly to the esophagus anteriorly.
b. The oropharynx is continuous superiorly with the nasopharynx.
c. The nasopharynx is involved in digestion.
d. The laryngopharynx is composed partially of cartilage.

**17.** Which structure is located where the esophagus penetrates the diaphragm?
a. esophageal hiatus
b. cardiac orifice
c. upper esophageal sphincter
d. lower esophageal sphincter

**18.** Which phase of deglutition involves contraction of the longitudinal muscle layer of the muscularis?
a. voluntary phase
b. buccal phase
c. pharyngeal phase
d. esophageal phase

**19.** Which of these cells secrete hormones?
a. parietal cells
b. mucous neck cells
c. enteroendocrine cells
d. chief cells

**20.** Where does the majority of chemical digestion in the stomach occur?
a. fundus and body
b. cardia and fundus
c. body and pylorus
d. body

**21.** During gastric emptying, chyme is released into the duodenum through the _____.
a. esophageal hiatus
b. pyloric antrum
c. pyloric canal
d. pyloric sphincter

**22.** Parietal cells secrete _____.
a. gastrin
b. hydrochloric acid
c. pepsin
d. pepsinogen

**23.** In which part of the alimentary canal does most digestion occur?
a. stomach
b. proximal small intestine
c. distal small intestine
d. ascending colon

**24.** Which of these is most associated with villi?
a. haustra
b. lacteals
c. bacterial flora
d. intestinal glands

**25.** What is the role of the small intestine's MALT?
a. secreting mucus
b. buffering acidic chyme
c. activating pepsin
d. preventing bacteria from entering the bloodstream

**26.** Which part of the large intestine attaches to the appendix?
a. cecum
b. ascending colon
c. transverse colon
d. descending colon

**27.** Which of these statements about bile is true?
a. About 500 mL is secreted daily.
b. Its main function is the denaturation of proteins.
c. It is synthesized in the gallbladder.
d. Bile salts are recycled.

**28.** Pancreatic juice _____.
a. deactivates bile.
b. is secreted by pancreatic islet cells.
c. buffers chyme.
d. is released into the cystic duct.

**29.** Where does the chemical digestion of starch begin?
a. mouth
b. esophagus
c. stomach
d. small intestine

**30.** Which of these is involved in the chemical digestion of protein?
a. pancreatic amylase
b. trypsin
c. sucrase
d. pancreatic nuclease

**31.** Where are most fat-digesting enzymes produced?
a. small intestine
b. gallbladder
c. liver
d. pancreas

**32.** Which of these nutrients is absorbed mainly in the duodenum?
a. glucose
b. iron
c. sodium
d. 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 $B_{12}$ 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 have more lean muscle mass then 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.

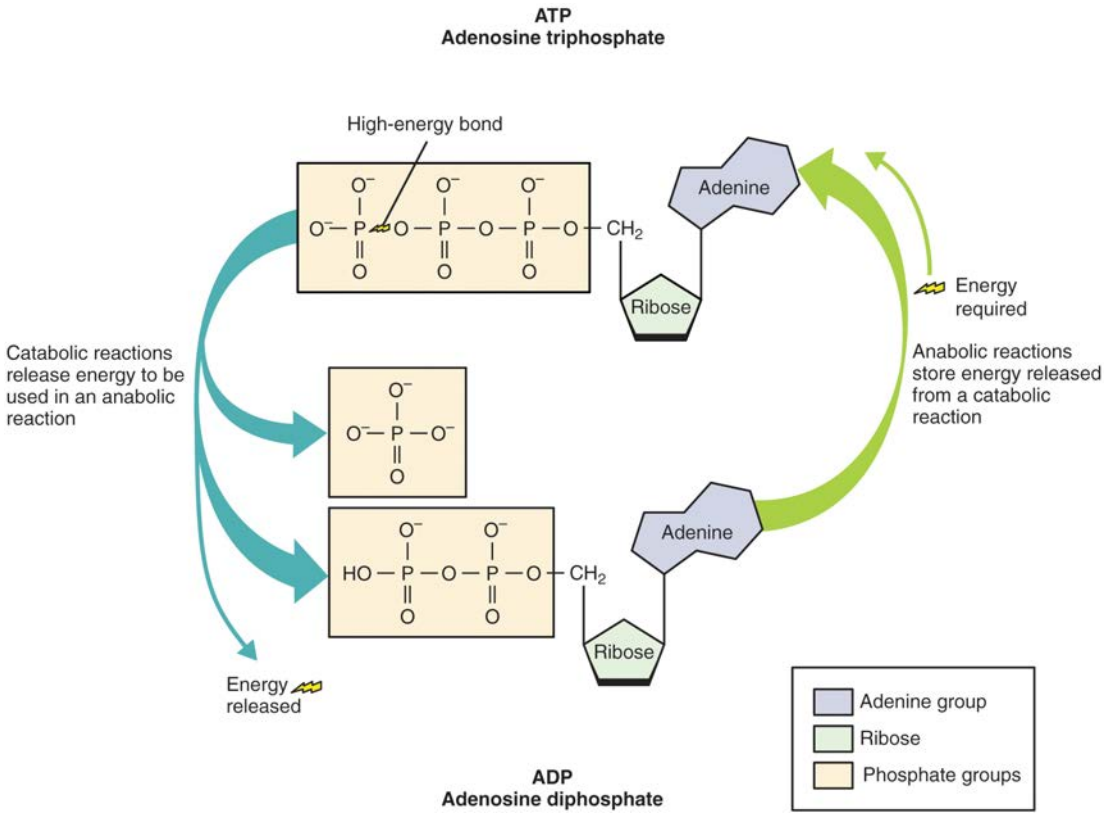



**Figure 24.2 Structure of ATP Molecule** Adenosine triphosphate (ATP) is the energy molecule of the cell. During catabolic reactions, ATP is created and energy is stored until needed during anabolic reactions.

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**).

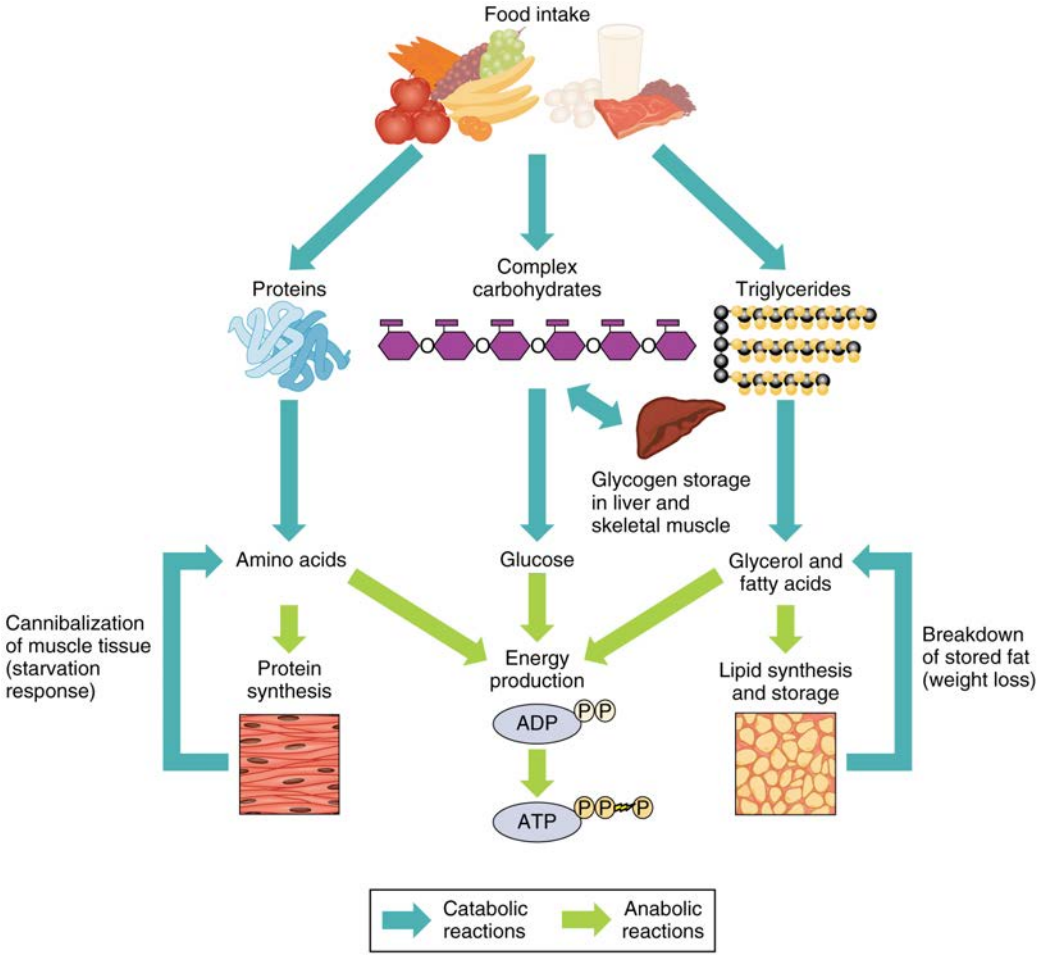



**Figure 24.3 Sources of ATP** During catabolic reactions, proteins are broken down into amino acids, lipids are broken down into fatty acids, and polysaccharides are broken down into monosaccharides. These building blocks are then used for the synthesis of molecules in anabolic reactions.

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 β-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 glucagon; 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 **$FADH_2$**, 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.

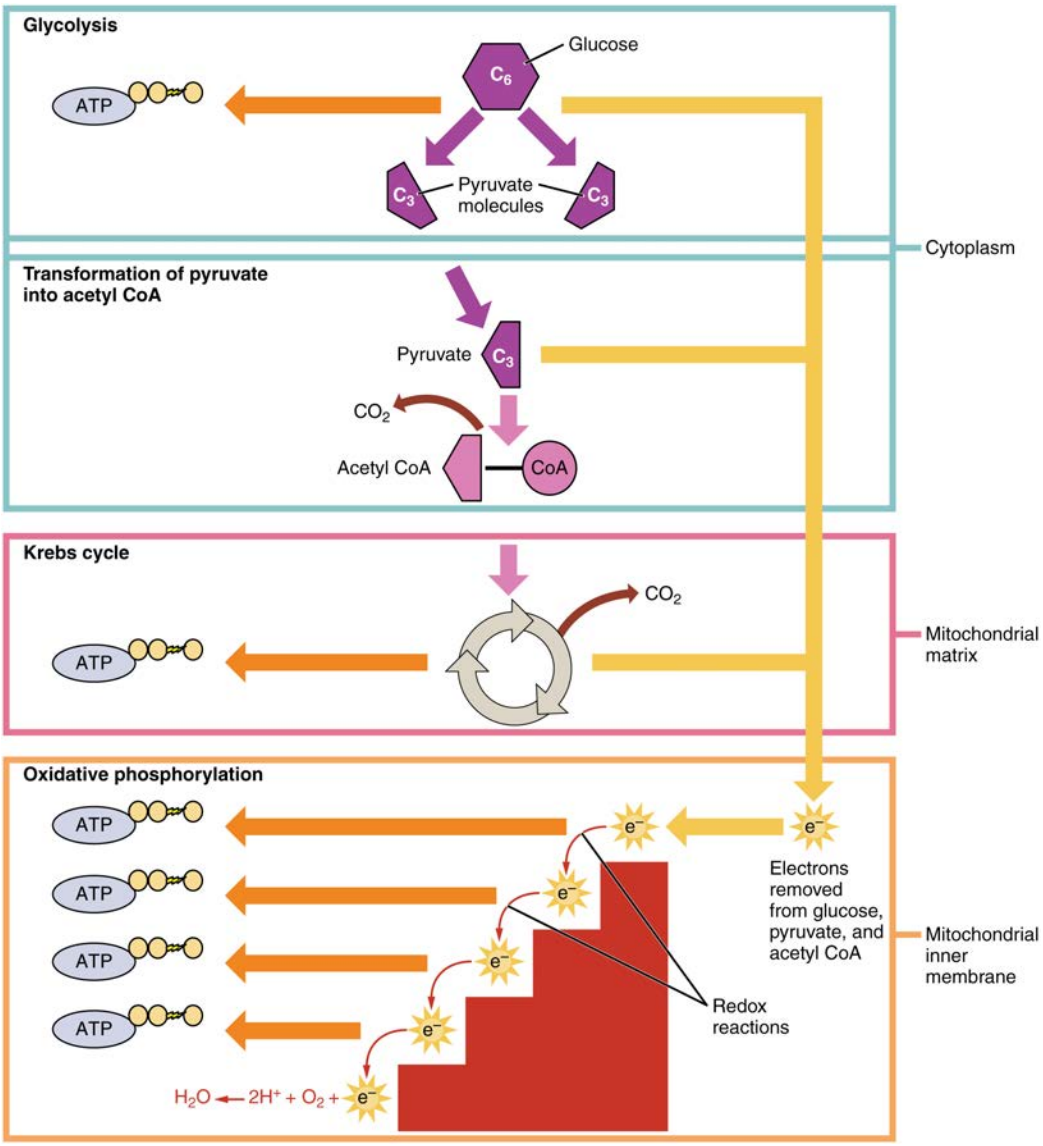



**Figure 24.4 Cellular Respiration** Cellular respiration oxidizes glucose molecules through glycolysis, the Krebs cycle, and oxidative phosphorylation to produce ATP.

## 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 phosphofructokinase, 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.

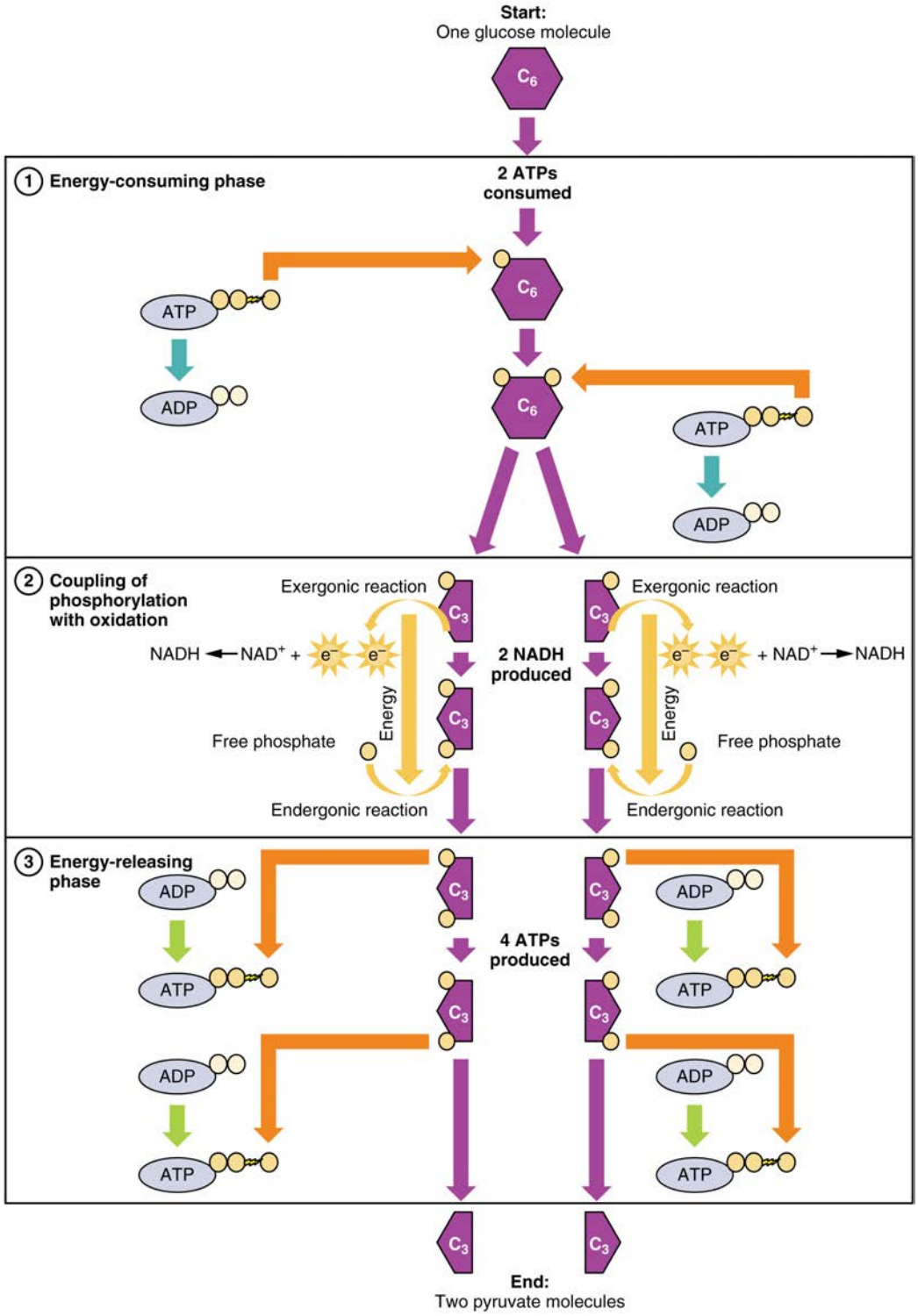



**Figure 24.5 Glycolysis Overview** During the energy-consuming phase of glycolysis, two ATPs are consumed, transferring two phosphates to the glucose molecule. The glucose molecule then splits into two three-carbon compounds, each containing a phosphate. During the second phase, an additional phosphate 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)** 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:

$$\text{Glucose} + 2\text{ATP} + 2\text{NAD}^+ + 4\text{ADP} + 2\text{P}_i \rightarrow 2\ \text{Pyruvate} + 4\text{ATP} + 2\text{NADH} + 2\text{H}^+$$

This equation states that glucose, in combination with ATP (the energy source), $NAD^+$ (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 $NAD^+$ 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 $NAD^+$ 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 $NAD^+$, GDP, and FAD, with carbon dioxide being a “waste product” (**Figure 24.6**). The NADH and $FADH_2$ 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.

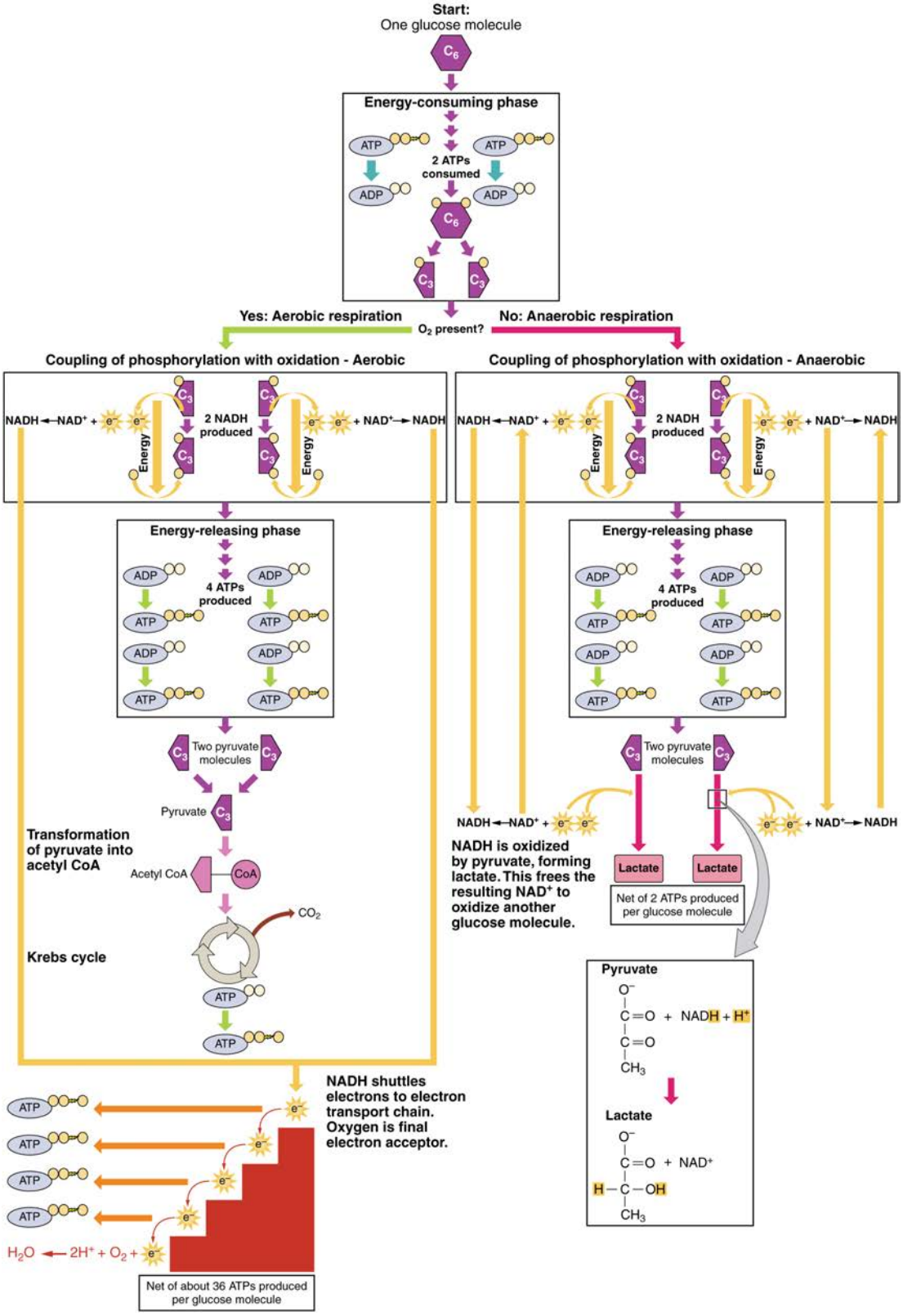



**Figure 24.6 Aerobic versus Anaerobic Respiration** The process of anaerobic respiration converts glucose into two lactate molecules in the absence of oxygen or within erythrocytes that lack mitochondria. During aerobic respiration, glucose is oxidized into two pyruvate molecules.

## 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 $FADH_2$, are created. NADH and $FADH_2$ then pass electrons through the electron transport chain in the mitochondria to generate more ATP molecules.

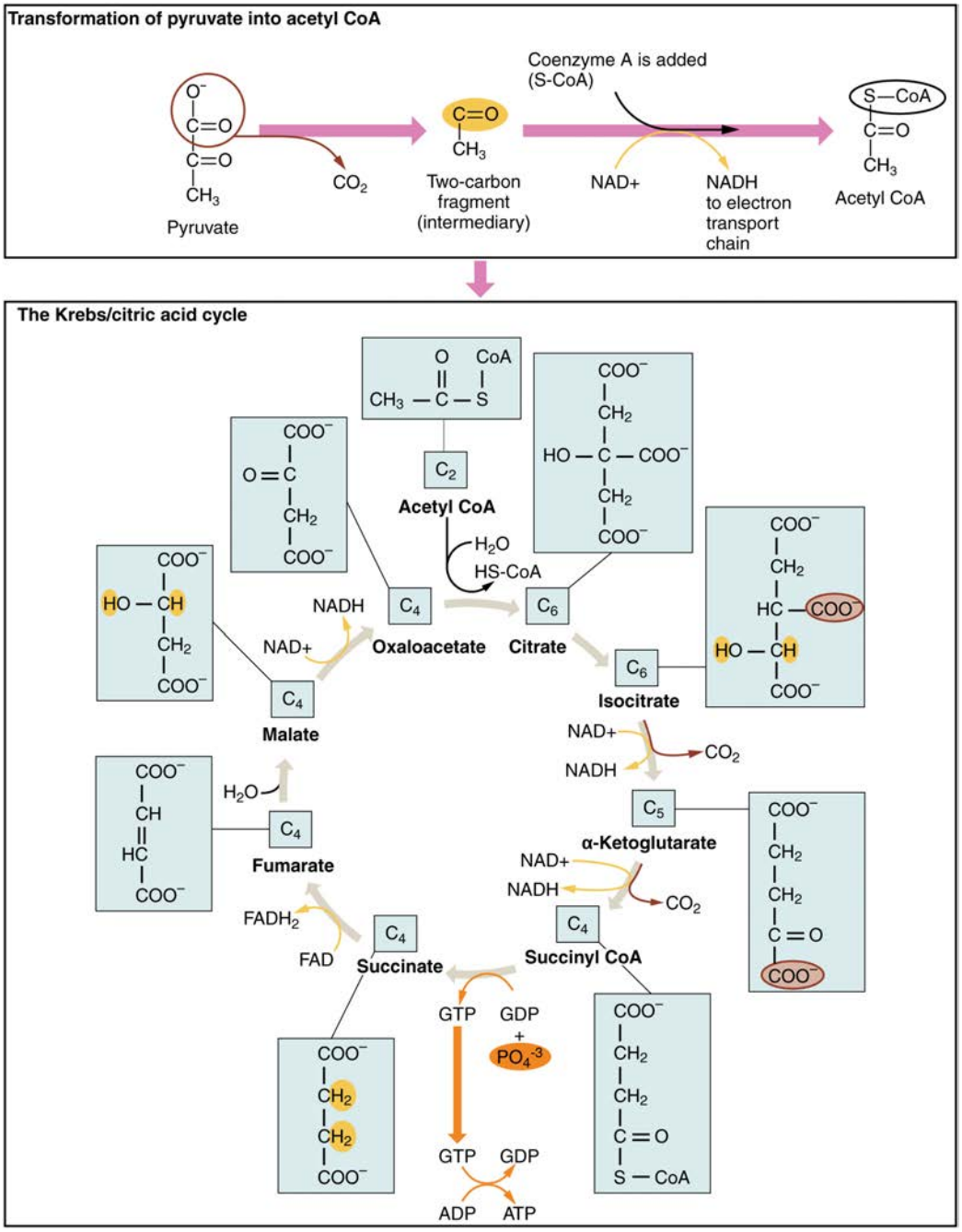



**Figure 24.7 Krebs Cycle** During the Krebs cycle, each pyruvate that is generated by glycolysis is converted into a two-carbon acetyl CoA molecule. The acetyl CoA is systematically processed through the cycle and produces high-energy NADH, $FADH_2$, and ATP molecules.

**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 $NAD^+$ 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 $FADH_2$, and three NADH. The $FADH_2$ 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 $CO_2$ and two NADH molecules are produced when isocitrate dehydrogenase converts isocitrate into the five-carbon α-ketoglutarate, which is then catalyzed and converted into the four-carbon succinyl CoA by α-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 $FADH_2$. Fumarase then converts fumarate into malate, which malate dehydrogenase then converts back into oxaloacetate while reducing $NAD^+$ 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 $FADH_2$ are created. Each carbon of pyruvate is converted into $CO_2$, 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 $FADH_2$ produced by the Krebs cycle to generate ATP. Electrons from NADH and $FADH_2$ 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 $H^+$ 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 $O_2$) with the transfer of protons ($H^+$ 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, $O_2$, 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, $O_2$, and $H^+$ 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.

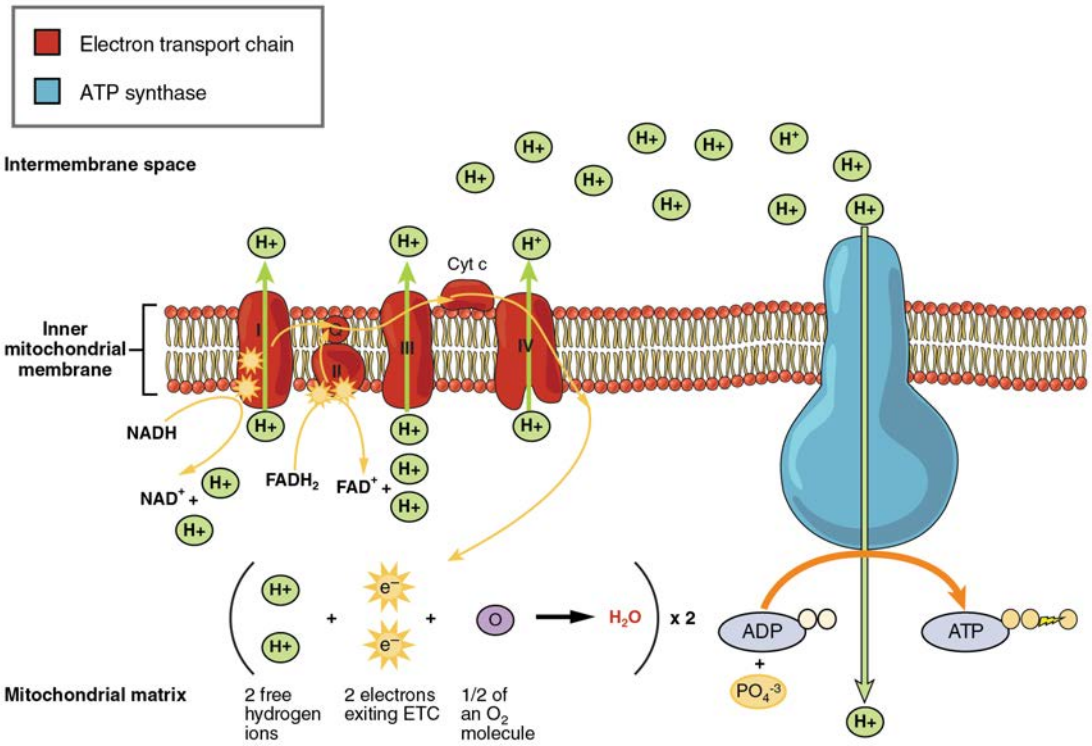



**Figure 24.8 Electron Transport Chain** The electron transport chain is a series of electron carriers and ion pumps that are used to pump $H^+$ ions out of the inner mitochondrial matrix.

## Interactive LINK

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

The electrons released from NADH and $FADH_2$ 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 $H^+$ 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 $H^+$ ions across the inner membrane down a gradient and into the mitochondrial matrix. As the $H^+$ ions traverse the complex, the shaft of the complex rotates. This rotation enables other portions of ATP synthase to encourage ADP and $P_i$ 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 $FADH_2$ 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 $FADH_2$. The electrons from $FADH_2$ 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**).

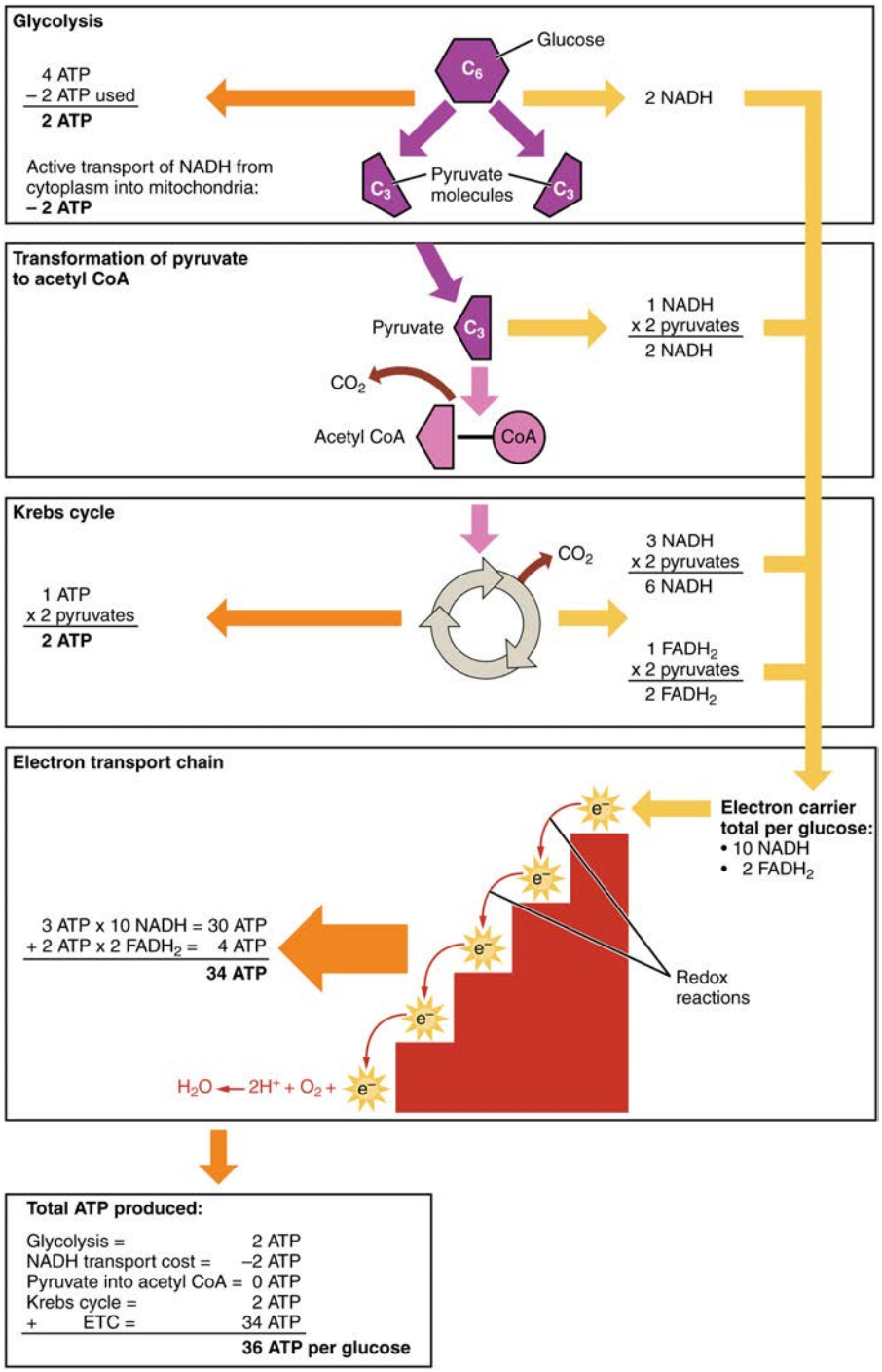



**Figure 24.9 Carbohydrate Metabolism** Carbohydrate metabolism involves glycolysis, the Krebs cycle, and the electron transport chain.

## 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.

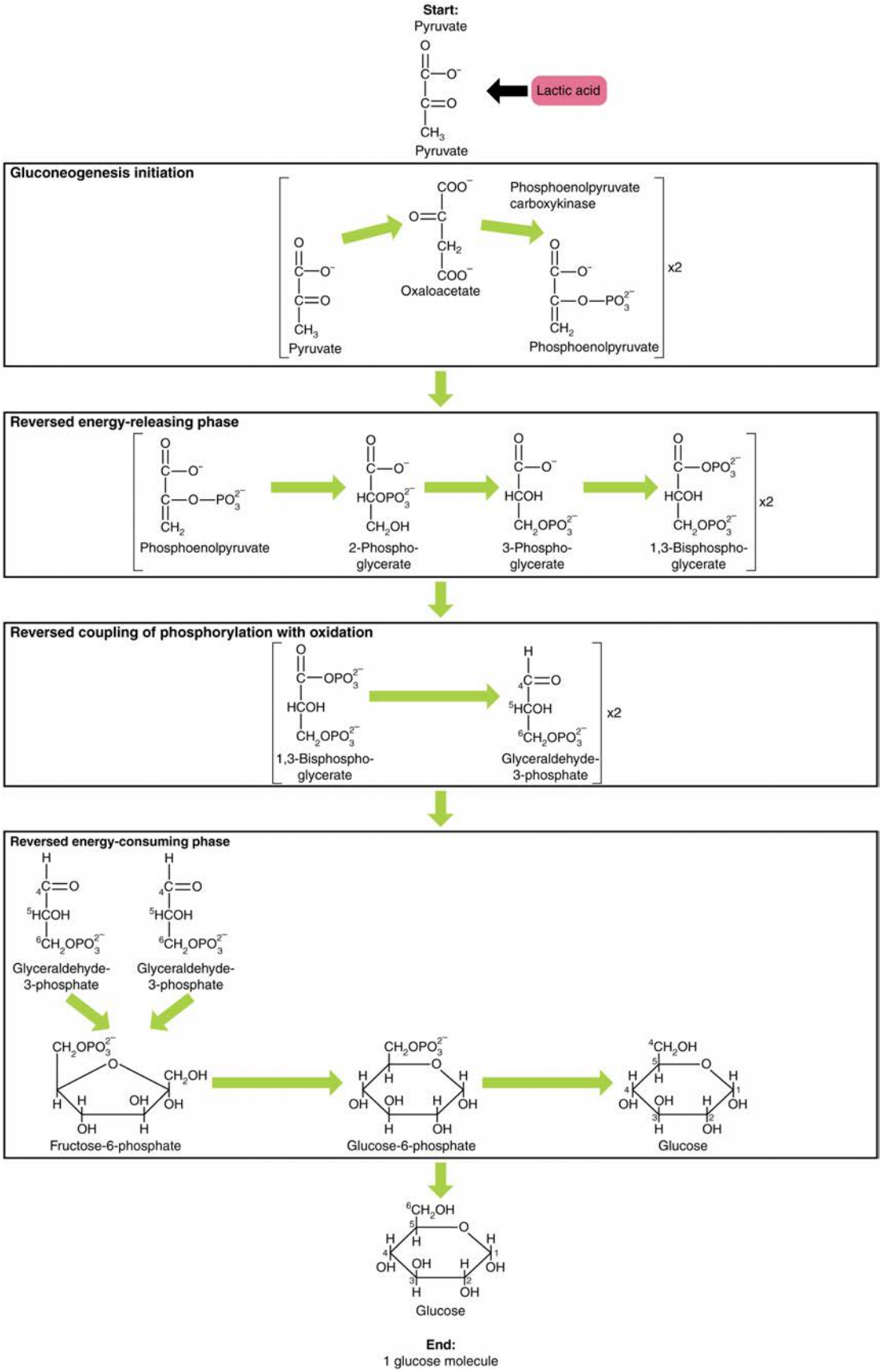



**Figure 24.10 Gluconeogenesis** Gluconeogenesis is the synthesis of glucose from pyruvate, lactate, glycerol, alanine, or glutamate.

Aging 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.

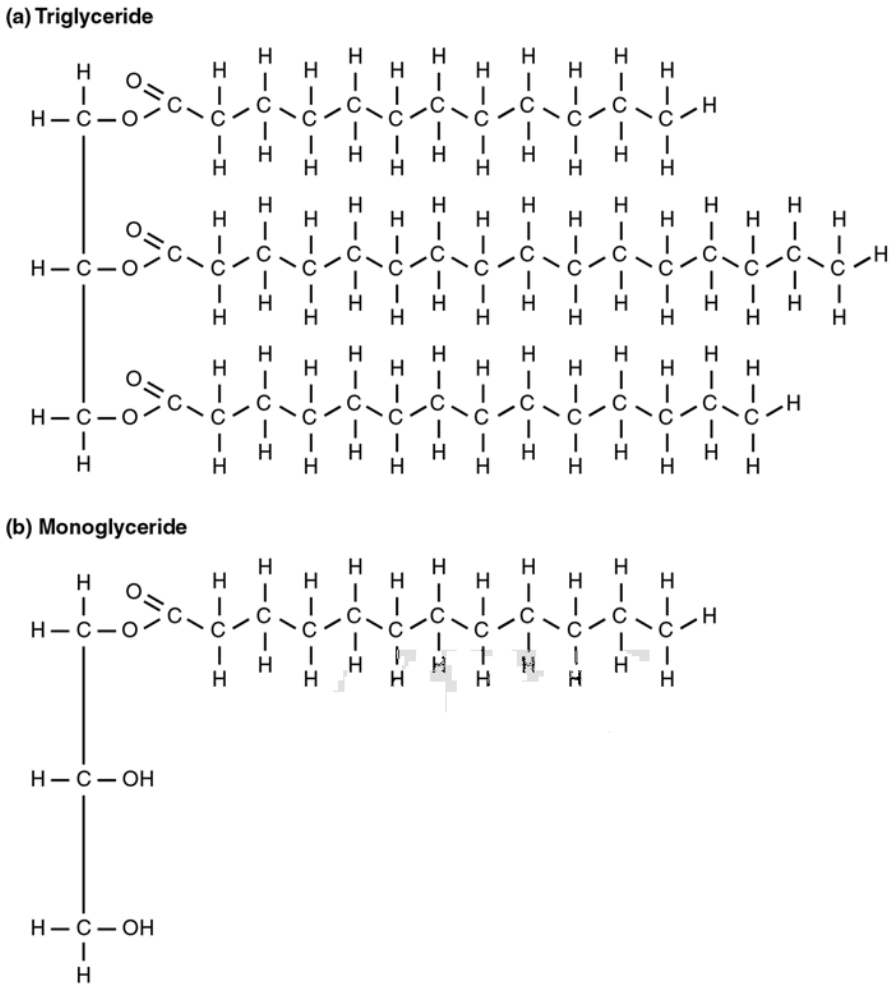



**Figure 24.11 Triglyceride Broken Down into a Monoglyceride** A triglyceride molecule (a) breaks down into a monoglyceride (b).

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.

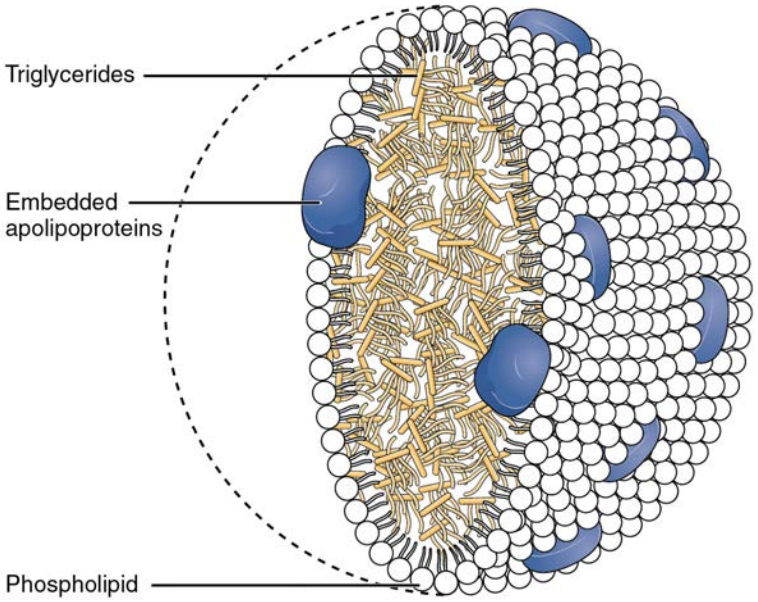



**Figure 24.12 Chylomicrons** Chylomicrons contain triglycerides, cholesterol molecules, and other apolipoproteins (protein molecules). They function to carry these water-insoluble molecules from the intestine, through the lymphatic system, and into the bloodstream, which carries the lipids to adipose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

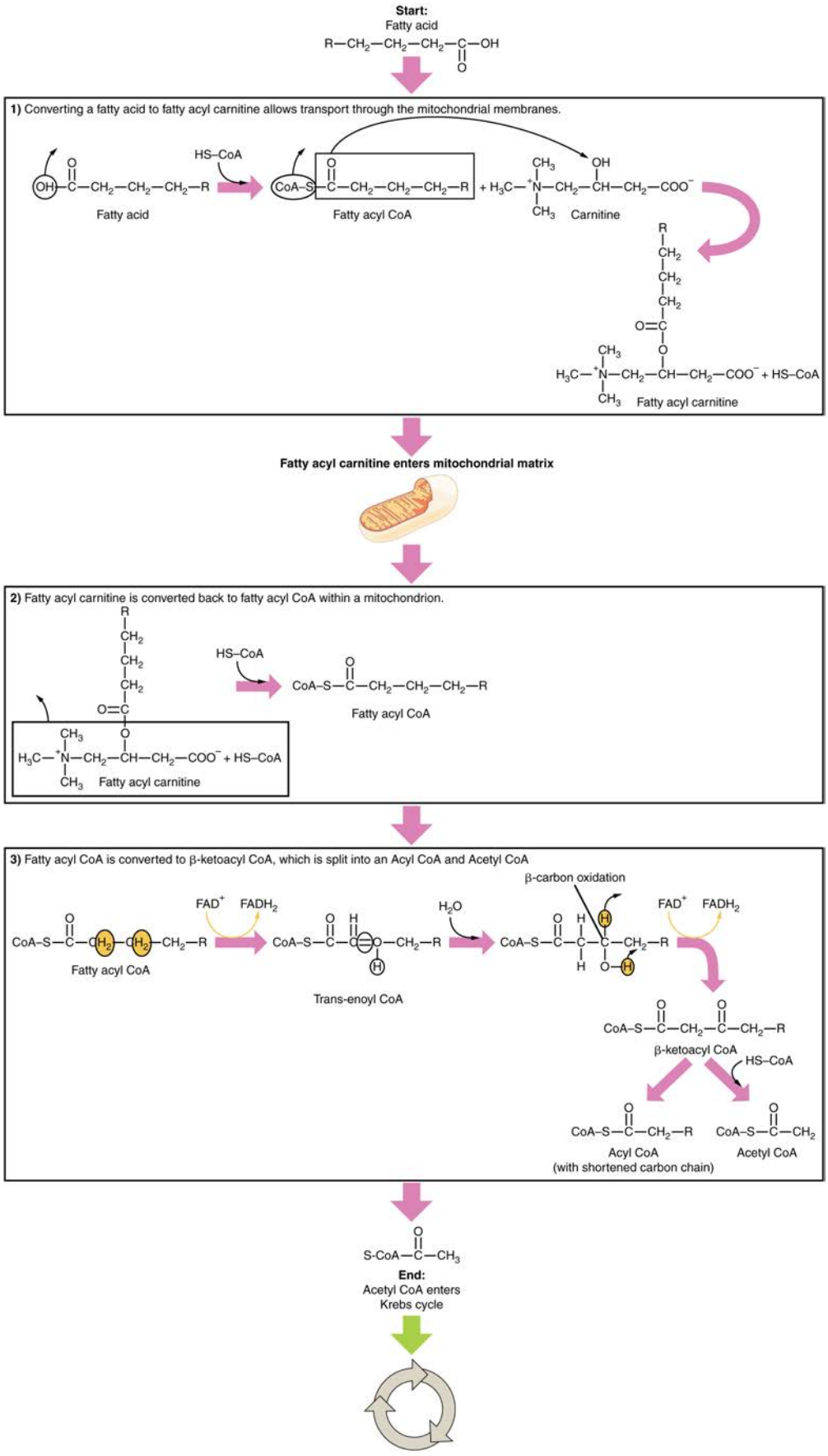



**Figure 24.13 Breakdown of Fatty Acids** During fatty acid oxidation, triglycerides can be broken down into acetyl CoA molecules and used for energy when glucose levels are low.

## 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 β-hydroxybutyrate, the primary ketone body in the blood (**Figure 24.14**).

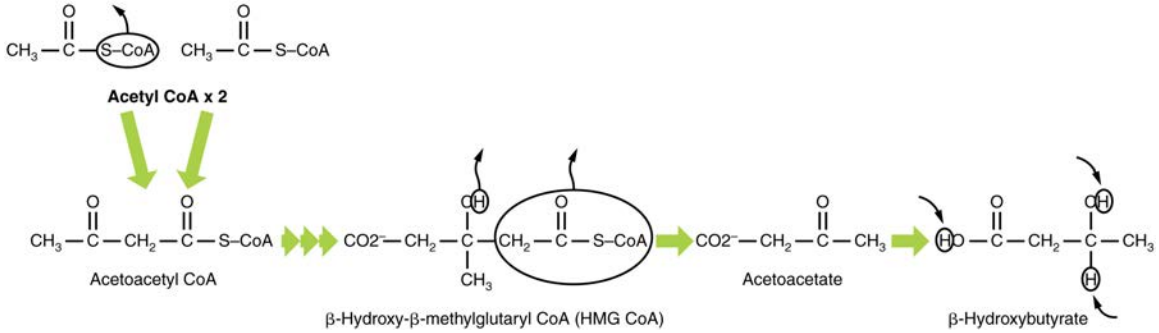



**Figure 24.14 Ketogenesis** Excess acetyl CoA is diverted from the Krebs cycle to the ketogenesis pathway. This reaction occurs in the mitochondria of liver cells. The result is the production of β-hydroxybutyrate, the primary ketone body found in the blood.

## 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 $CO_2$ 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 (β)-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**).

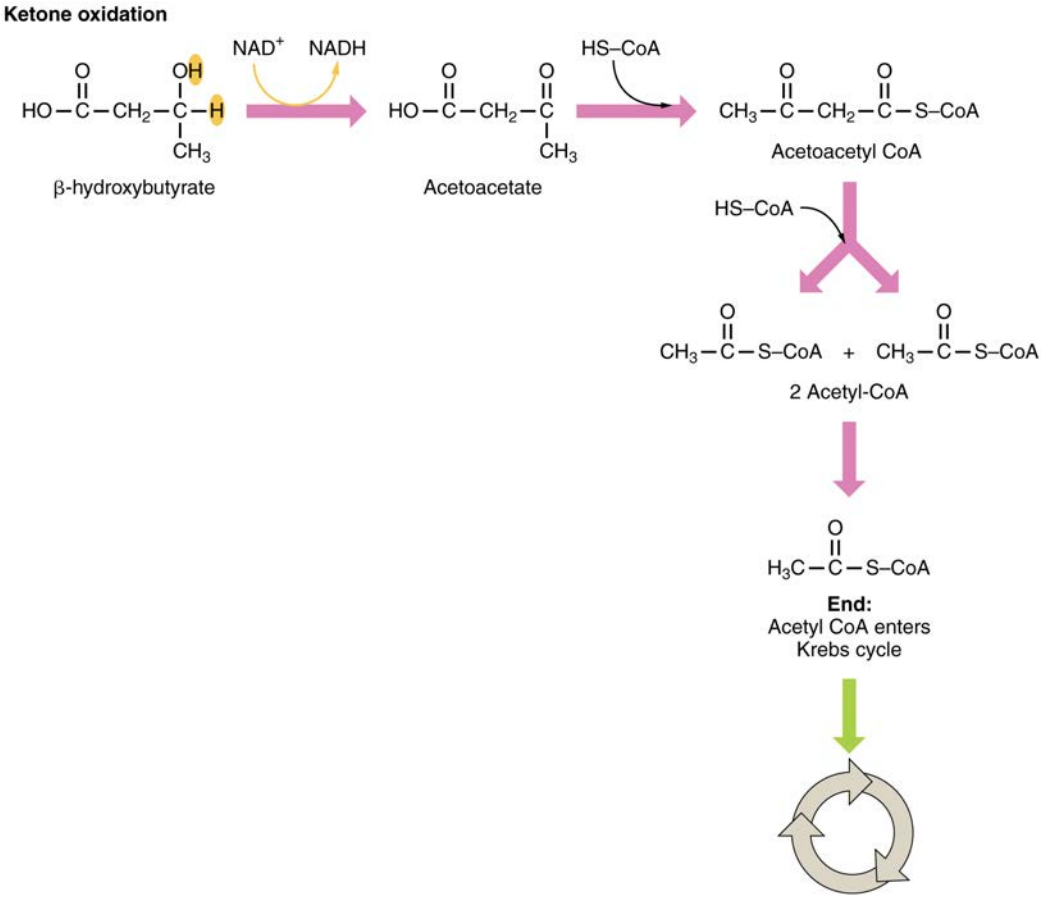



**Figure 24.15 Ketone Oxidation** When glucose is limited, ketone bodies can be oxidized to produce acetyl CoA to be used in the Krebs cycle to generate energy.

## 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.

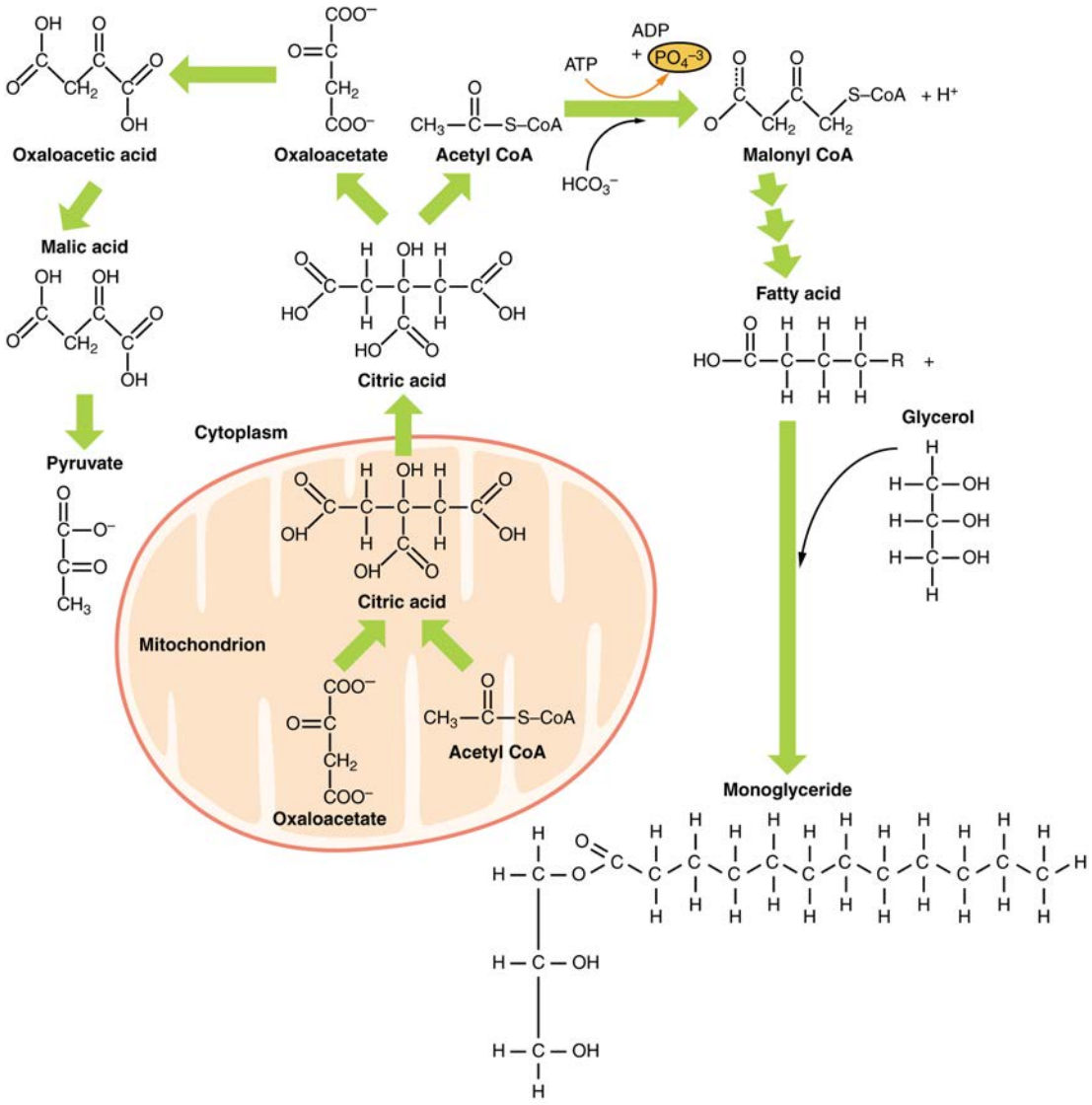



**Figure 24.16 Lipid Metabolism** Lipids may follow one of several pathways during metabolism. Glycerol and fatty acids follow different pathways.

## 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 $CO_2$ 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.

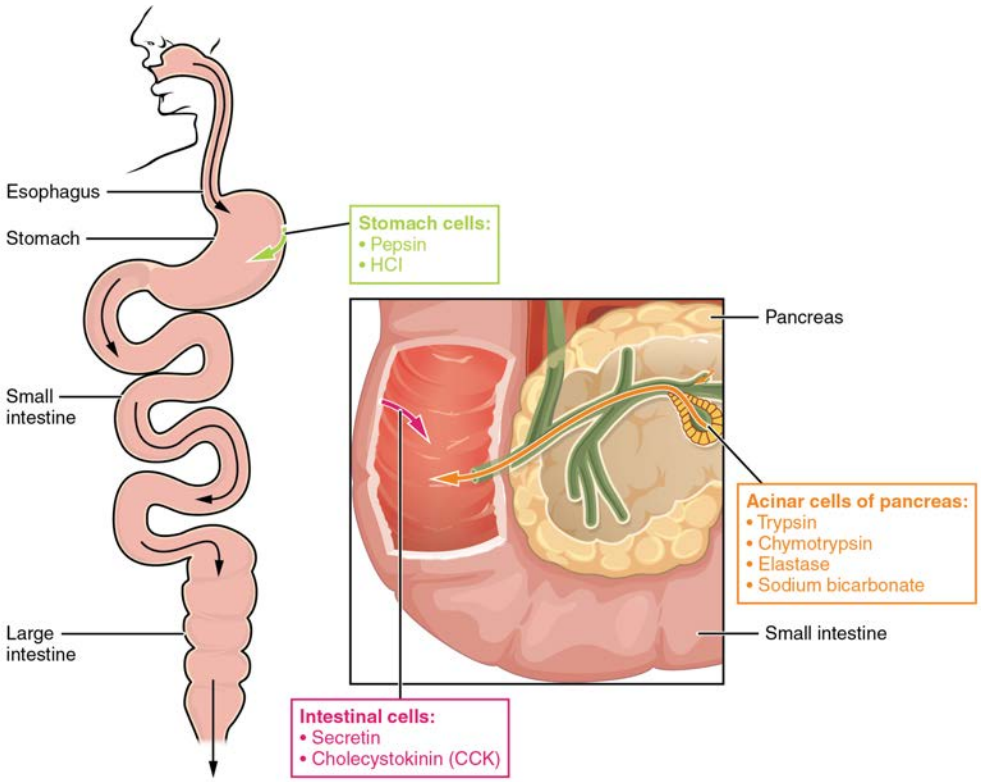



**Figure 24.17 Digestive Enzymes and Hormones** Enzymes in the stomach and small intestine break down proteins into amino acids. HCl in the stomach aids in proteolysis, and hormones secreted by intestinal cells direct the digestive processes.

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 $CO_2$, resulting in urea and water. The urea is eliminated through the kidneys in the urine (**Figure 24.18**).

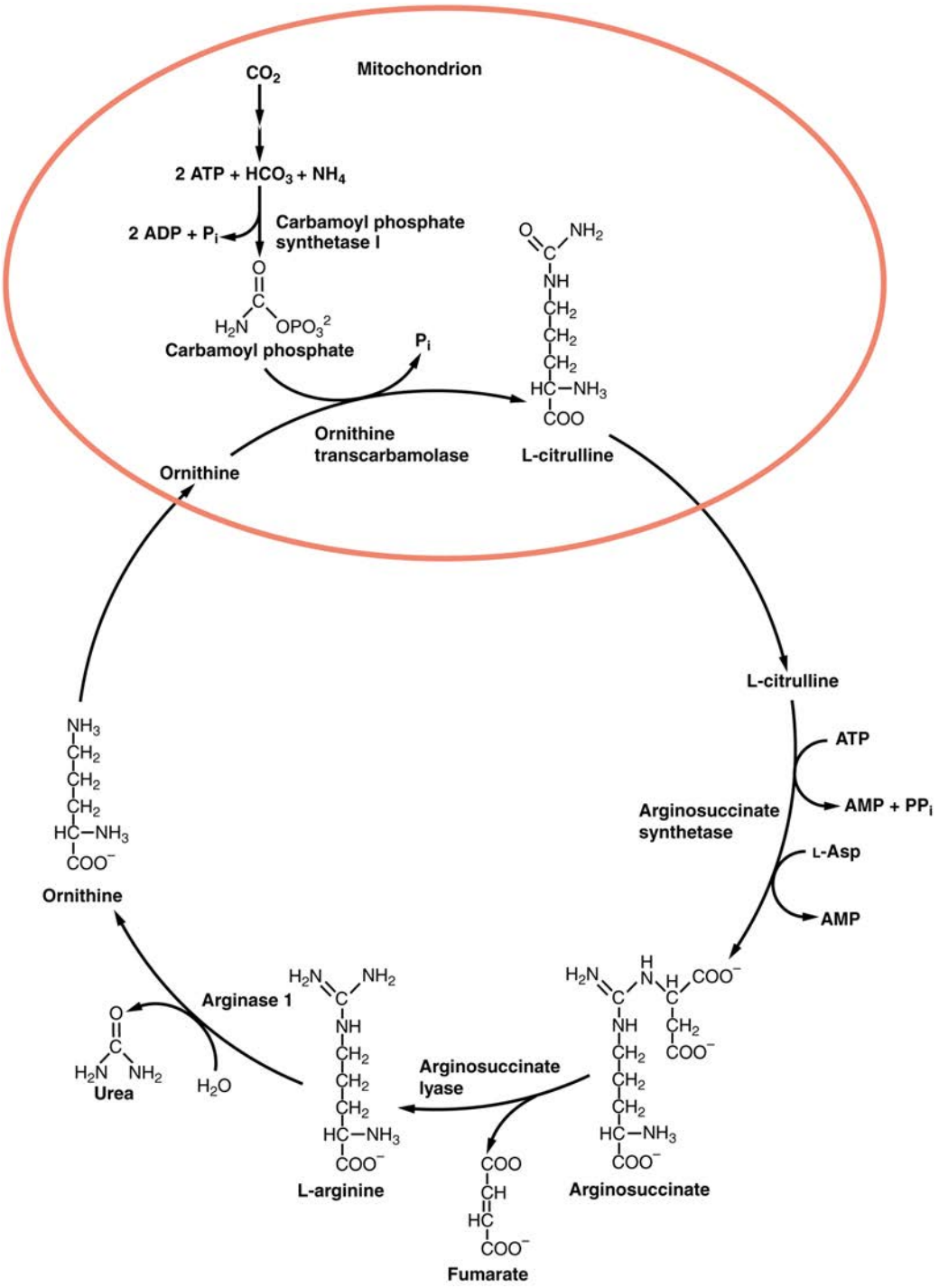



**Figure 24.18 Urea Cycle** Nitrogen is transaminated, creating ammonia and intermediates of the Krebs cycle. Ammonia is processed in the urea cycle to produce urea that is eliminated through the kidneys.

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, acetoacyl CoA, oxaloacetate, and α-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.

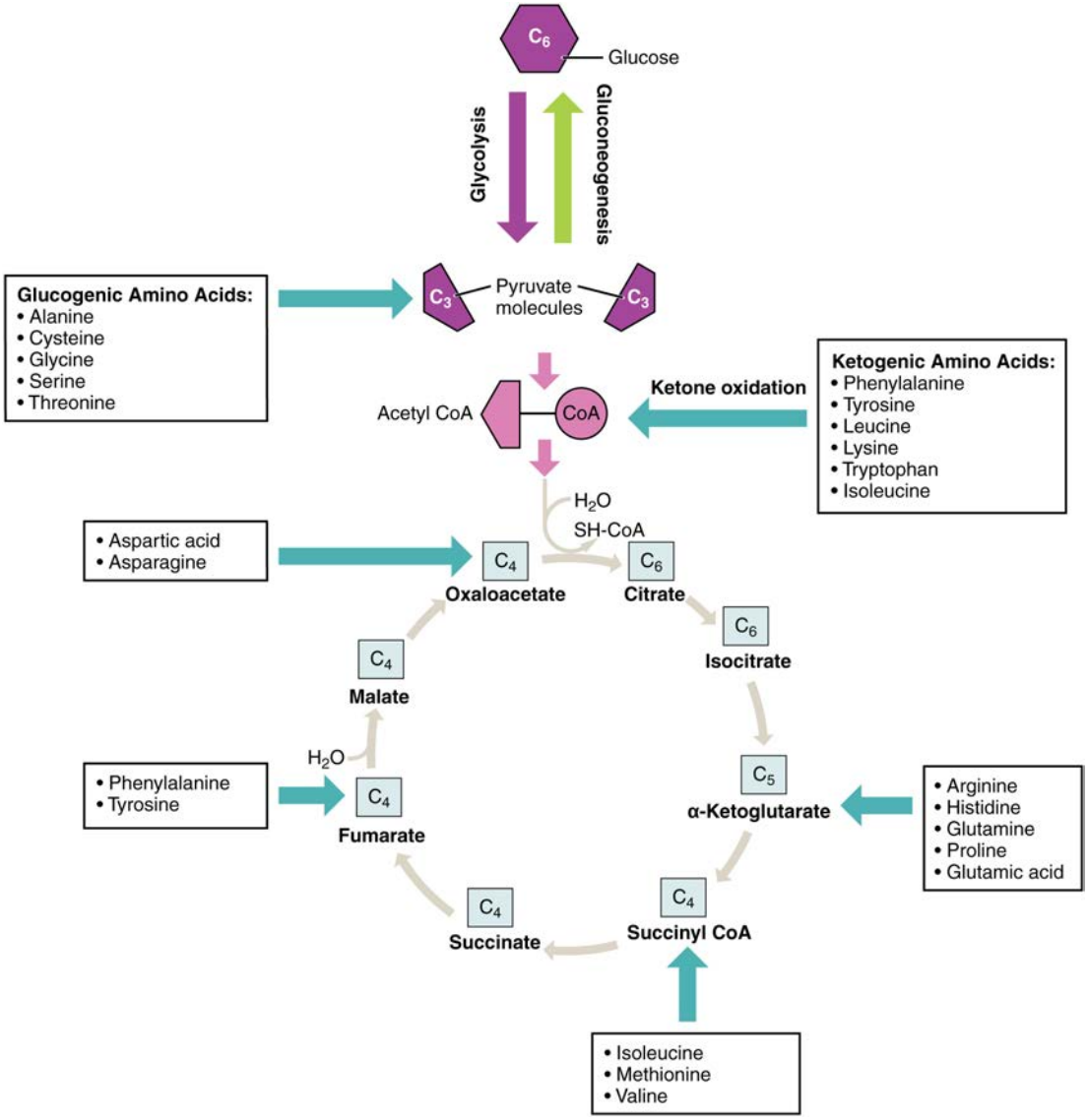



**Figure 24.19 Energy from Amino Acids** Amino acids can be broken down into precursors for glycolysis or the Krebs cycle. Amino acids (in bold) can enter the cycle through more than one pathway.

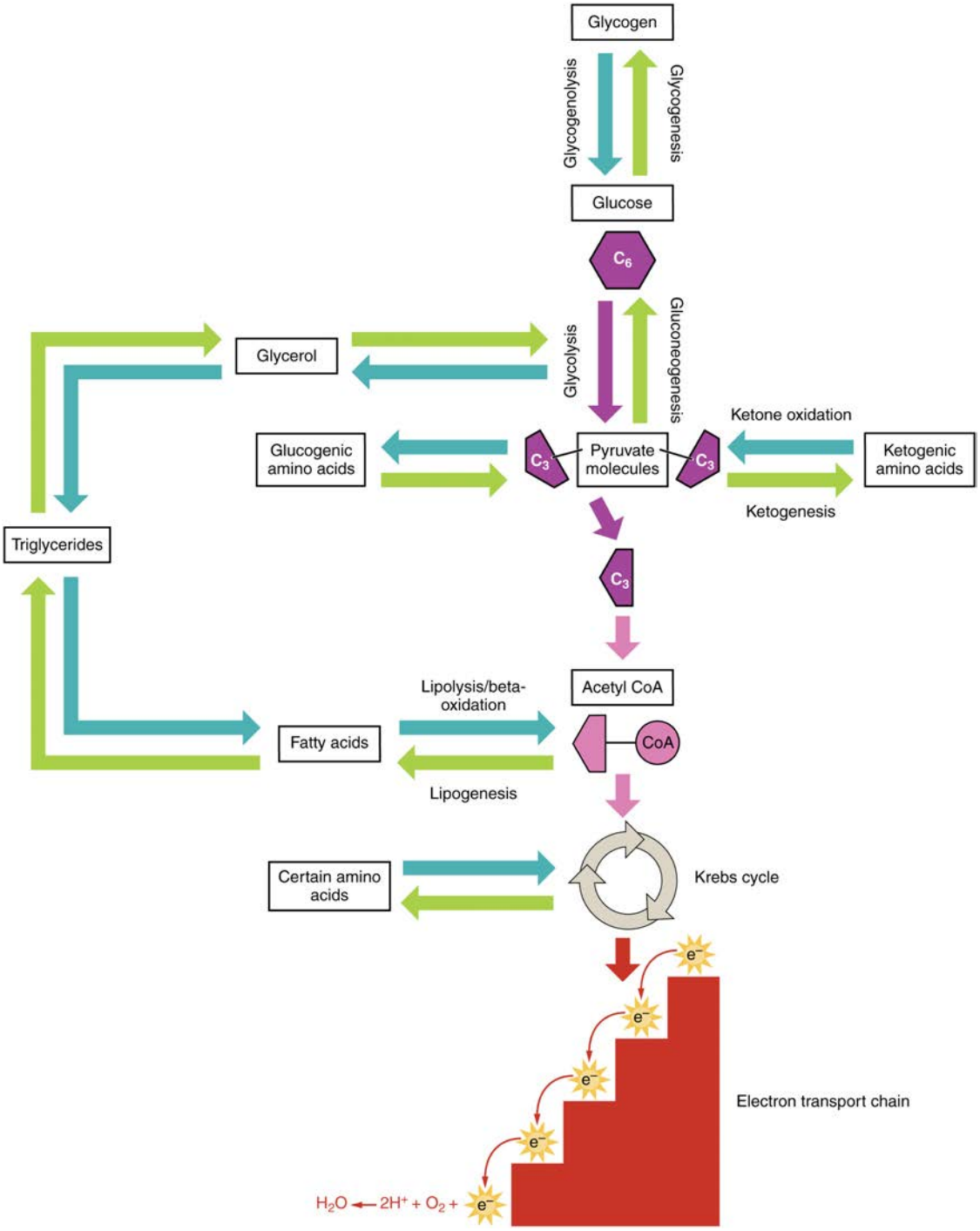



**Figure 24.20 Catabolic and Anabolic Pathways** Nutrients follow a complex pathway from ingestion through anabolism and catabolism to energy production.

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 (catabolism exceeds anabolism). 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.

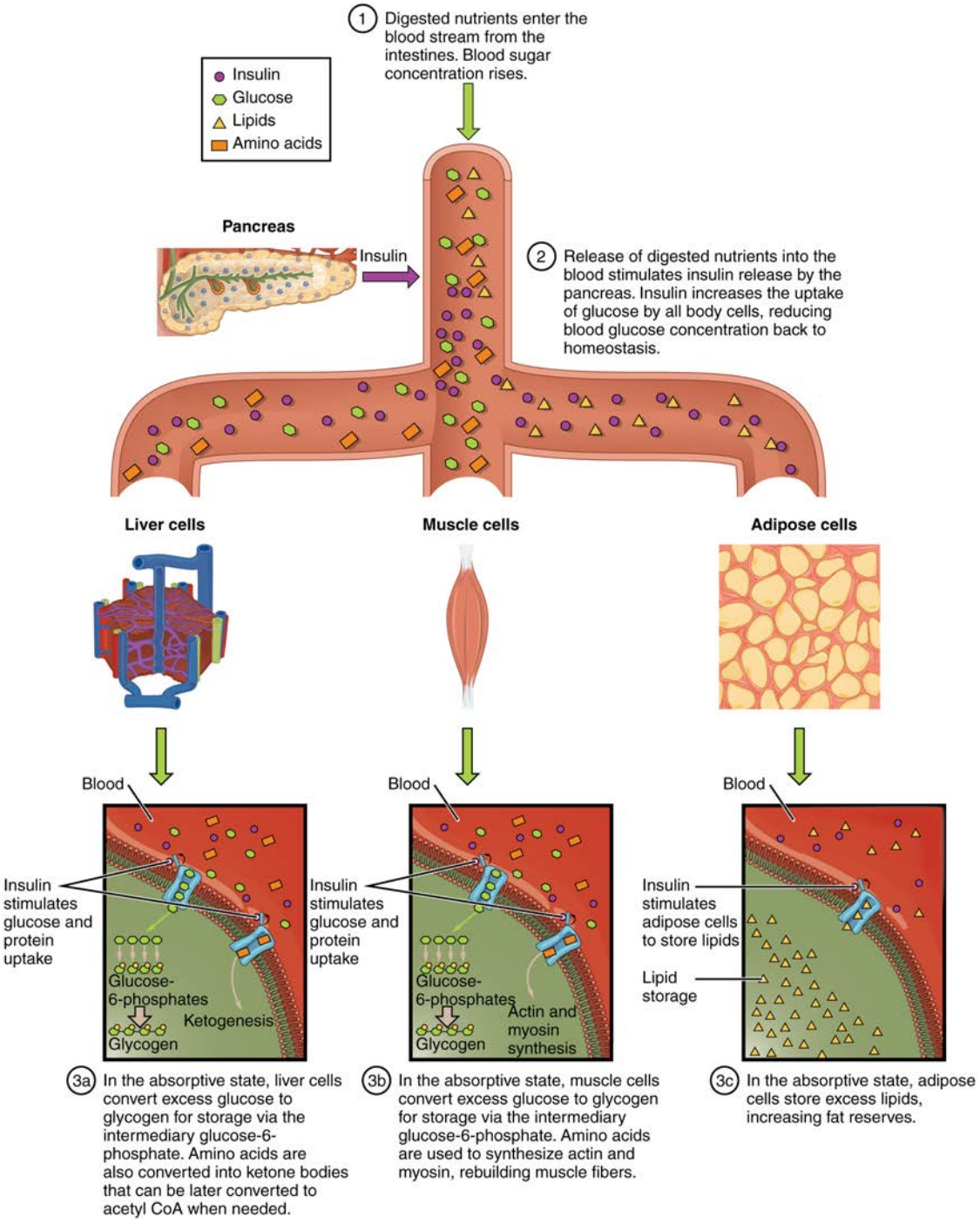



**Figure 24.21 Absorptive State** During the absorptive state, the body digests food and absorbs the nutrients.

## 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.

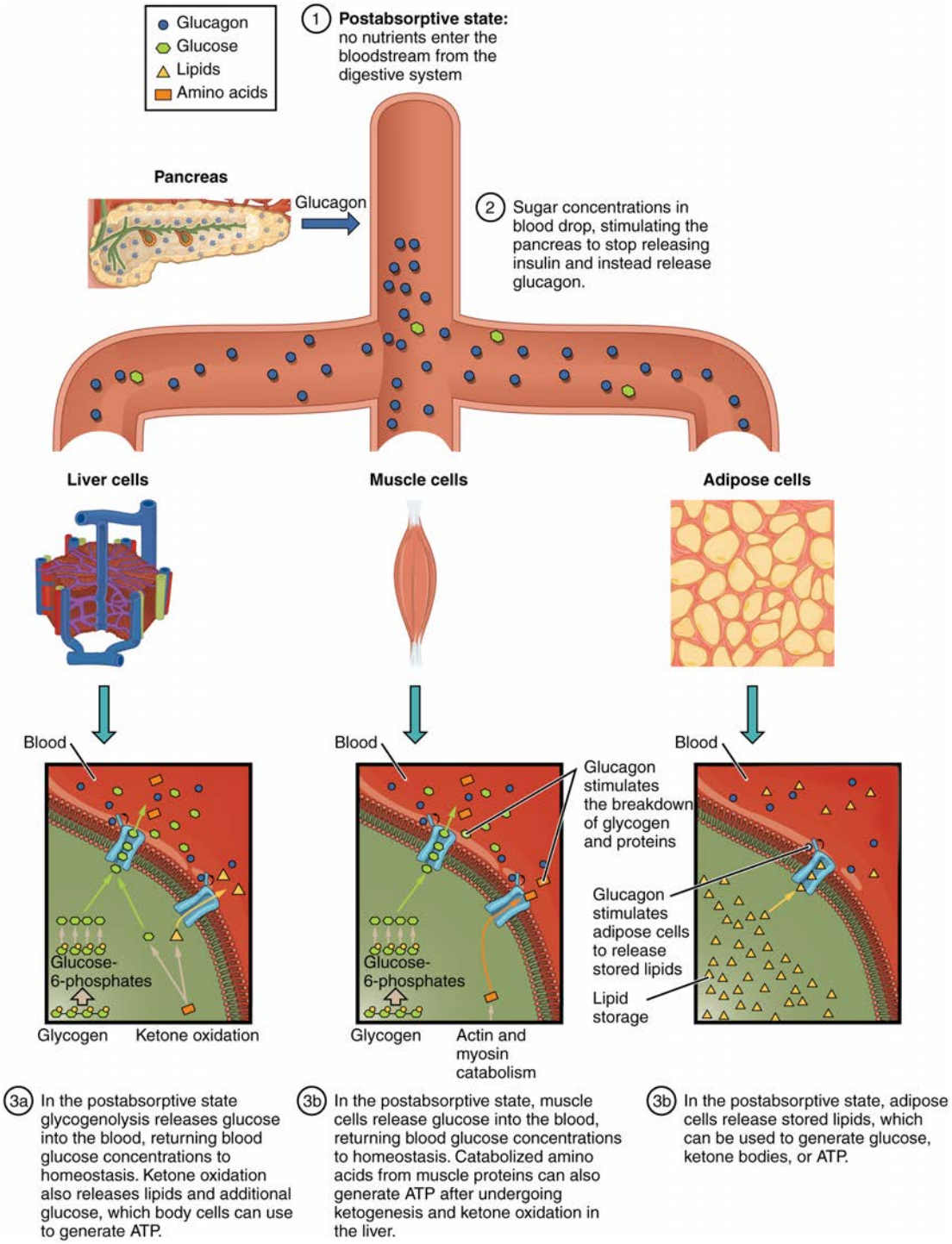



**Figure 24.22 Postabsorptive State** During the postabsorptive state, the body must rely on stored glycogen for energy.

### 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.

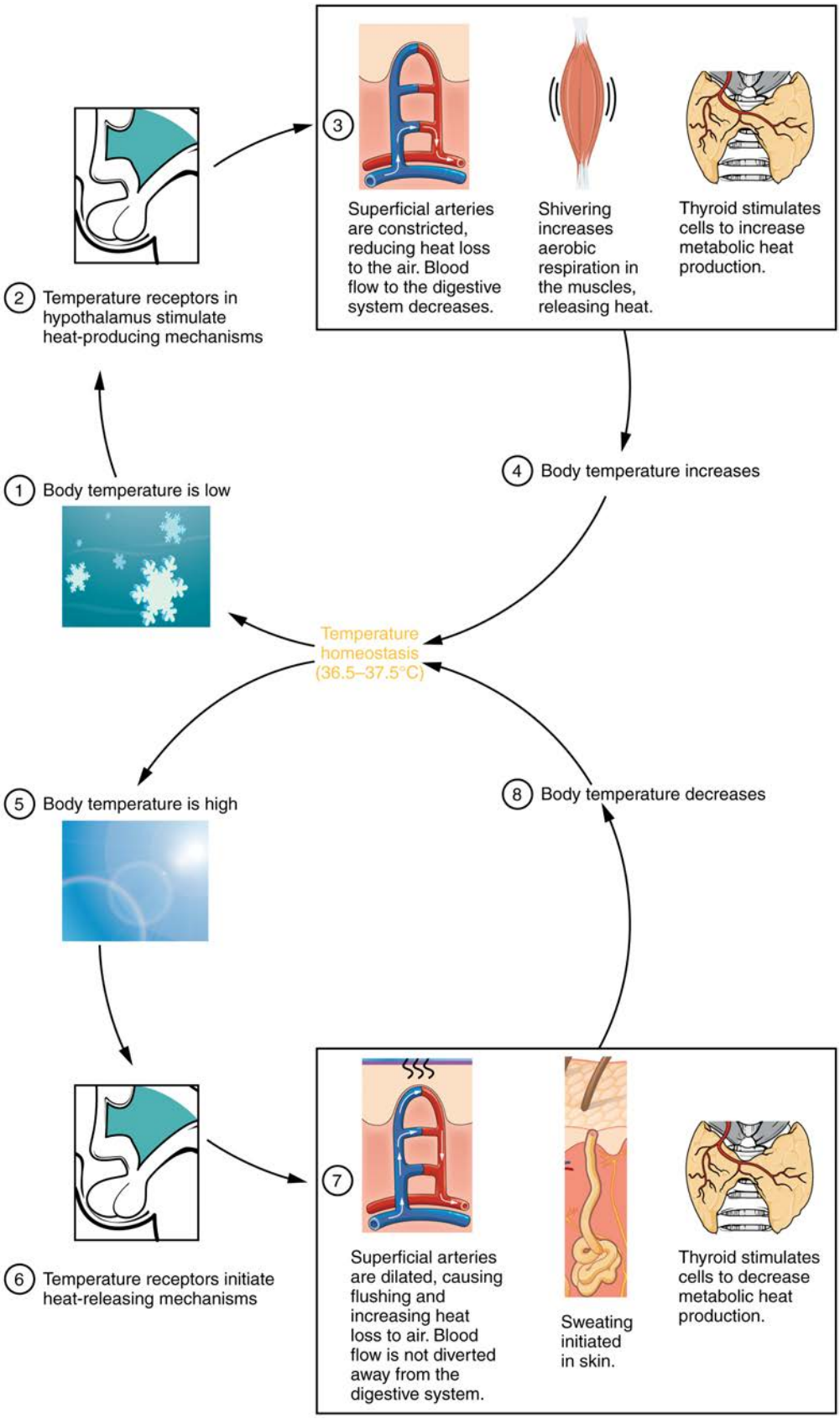



**Figure 24.23 Hypothalamus Controls Thermoregulation** The hypothalamus controls thermoregulation.

## 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. A **calorie** is the amount of heat it takes to raise 1 g of water by 1 °C. 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.

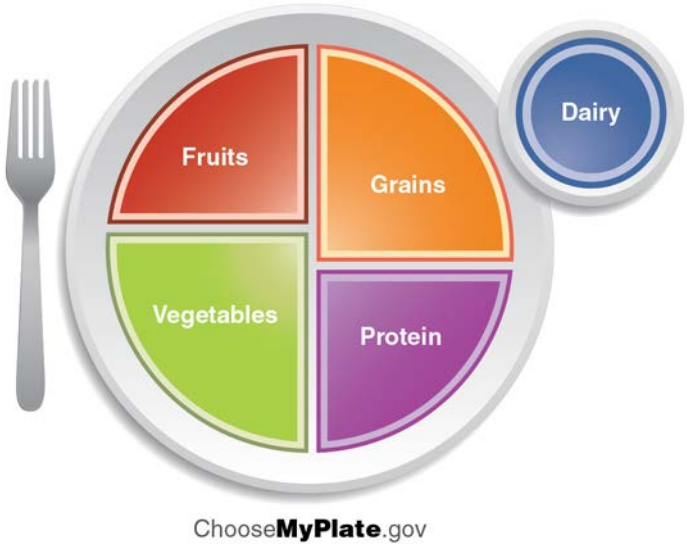



**Figure 24.24 MyPlate** The U.S. Department of Agriculture developed food guidelines called MyPlate to help demonstrate how to maintain a healthy lifestyle.

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 $kg/m^2$. Overweight is defined as a BMI of 25 to 29.9 $kg/m^2$, and obesity is considered to be a BMI greater than 30 $kg/m^2$. 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 β-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<br>retinal or β-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 |
| D<br>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<br>tocopherols | Seeds, nuts, vegetable oils, avocados, wheat germ | 15 mg | Antioxidant | Anemia |
| K<br>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 |
|---|---|---|---|---|
| $B_1$<br>thiamine | Whole grains, enriched bread and cereals, milk, meat | 1.1–1.2 mg | Carbohydrate metabolism | Beriberi, Wernicke-Korsikoff syndrome |

Table 24.4

**Water-soluble Vitamins**

| Vitamin and alternative name | Sources | Recommended daily allowance | Function | Problems associated with deficiency |
|---|---|---|---|---|
| $B_2$ 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 |
| $B_3$ 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 |
| $B_5$ 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 |
| $B_6$ 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 |
| $B_7$ biotin | Liver, fruits, meats | 30 $\mu$g | Cell growth, metabolism of fatty acids, production of blood cells | Rare in developed countries; symptoms include dermatitis, hair loss, loss of muscular coordination |
| $B_9$ folic acid | Liver, legumes, dark green leafy vegetables, enriched breads and cereals, citrus fruits | 400 $\mu$g | DNA/protein synthesis | Poor growth, gingivitis, appetite loss, shortness of breath, gastrointestinal problems, mental deficits |
| $B_{12}$ cyanocobalamin | Fish, meat, poultry, dairy products, eggs | 2.4 $\mu$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 phosphorous, 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 |

Table 24.6

## Trace Minerals

| Mineral | Sources | Recommended daily allowance | Function | Problems associated with deficiency |
|---|---|---|---|---|
| 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 |
| Copper | Seafood, organ meats, nuts, legumes, chocolate, enriched breads and cereals, some fruits and vegetables | 900 $\mu$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 $\mu$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 $B_{12}$ | None |
| Selenium | Brewer's yeast, wheat germ, liver, butter, fish, shellfish, whole grains | 55 $\mu$g | Antioxidant, thyroid function, immune system function | Muscle pain |
| Chromium | Whole grains, lean meats, cheese, black pepper, thyme, brewer's yeast | 25–35 $\mu$g | Insulin function | High blood sugar, triglyceride, and cholesterol levels |
| Molybdenum | Legumes, whole grains, nuts | 45 $\mu$g | Cofactor for enzymes | Rare |

**Table 24.6**

## KEY TERMS

**ATP synthase** protein pore complex that creates ATP

**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

**basal metabolic rate (BMR)** amount of energy expended by the body at rest

**beta (β)-hydroxybutyrate** primary ketone body produced in the body

**beta (β)-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 required raise 1 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 $CO_2$ and high-energy $FADH_2$, 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

**$FADH_2$** 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 $FADH_2$

**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

**Krebs cycle** also called the citric acid cycle or the tricarboxylic acid cycle, converts pyruvate into $CO_2$ and high-energy $FADH_2$, NADH, and ATP molecules

**ketone bodies** alternative source of energy when glucose is limited, created when too much acetyl CoA is created during fatty acid oxidation

**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-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

**oxidation** loss of an electron

**oxidative phosphorylation** process that converts high-energy NADH and $FADH_2$ 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 $CO_2$ and high-energy $FADH_2$, NADH, and ATP molecules

**triglycerides** lipids, or fats, consisting of three fatty acid chains attached to a glycerol backbone

**trypsinogen** proenzyme form of trypsin

**trypsin** pancreatic enzyme that activates chymotrypsin and digests protein

**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 $P_i$ 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 $FADH_2$ 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 β-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

**1.** A monosaccharide is formed from a polysaccharide in what kind of reaction?
- a. oxidation–reduction reaction
- b. anabolic reaction
- c. catabolic reaction
- d. biosynthetic reaction

**2.** If anabolic reactions exceed catabolic reactions, the result will be _____.
- a. weight loss
- b. weight gain
- c. metabolic rate change
- d. development of disease

**3.** When NAD becomes NADH, the coenzyme has been _____.
- a. reduced
- b. oxidized
- c. metabolized
- d. hydrolyzed

**4.** Anabolic reactions use energy by _____.
- a. turning ADP into ATP
- b. removing a phosphate group from ATP
- c. producing heat
- d. breaking down molecules into smaller parts

**5.** Glycolysis results in the production of two _____ molecules from a single molecule of glucose. In the absence of _____, the end product of glycolysis is _____.
- a. acetyl CoA, pyruvate, lactate
- b. ATP, carbon, pyruvate
- c. pyruvate, oxygen, lactate
- d. pyruvate, carbon, acetyl CoA

**6.** The Krebs cycle converts _____ through a cycle of reactions. In the process, ATP, _____, and _____ are produced.
- a. acetyl CoA; FAD, NAD
- b. acetyl CoA; $FADH_2$; NADH
- c. pyruvate; NAD; $FADH_2$
- d. pyruvate; oxygen; oxaloacetate

**7.** Which pathway produces the most ATP molecules?
- a. lactic acid fermentation
- b. the Krebs cycle
- c. the electron transport chain
- d. glycolysis

**8.** Aerobic cellular respiration results in the production of these two products.
- a. NADH and $FADH_2$
- b. ATP and pyruvate
- c. ATP and glucose
- d. ATP and $H_2O$

**9.** When $NAD^+$ becomes NADH, the coenzyme has been _____.
- a. reduced
- b. oxidized
- c. metabolized
- d. hydrolyzed

**10.** Lipids in the diet can be _____.
- a. broken down into energy for the body
- b. stored as triglycerides for later use
- c. converted into acetyl CoA
- d. all of the above

**11.** The gallbladder provides _____ that aid(s) in transport of lipids across the intestinal membrane.
- a. lipases
- b. cholesterol
- c. proteins
- d. bile salts

**12.** Triglycerides are transported by chylomicrons because _____.
- a. they cannot move easily in the blood stream because they are fat based, while the blood is water based
- b. they are too small to move by themselves
- c. the chylomicrons contain enzymes they need for anabolism
- d. they cannot fit across the intestinal membrane

**13.** Which molecule produces the most ATP?
- a. carbohydrates
- b. $FADH_2$
- c. triglycerides
- d. NADH

**14.** Which molecules can enter the Krebs cycle?
- a. chylomicrons
- b. acetyl CoA
- c. monoglycerides

d. ketone bodies

**15.** Acetyl CoA can be converted to all of the following except _____.
a. ketone bodies
b. fatty acids
c. polysaccharides
d. triglycerides

**16.** Digestion of proteins begins in the _____ where _____ and _____ mix with food to break down protein into _____.
a. stomach; amylase; HCl; amino acids
b. mouth; pepsin; HCl; fatty acids
c. stomach; lipase; HCl; amino acids
d. stomach; pepsin; HCl; amino acids

**17.** Amino acids are needed to _____.
a. build new proteins
b. serve as fat stores
c. supply energy for the cell
d. create red blood cells

**18.** If an amino acid is not used to create new proteins, it can be _____.
a. converted to acetyl CoA
b. converted to glucose or ketones
c. converted to nitrogen
d. stored to be used later

**19.** During the absorptive state, glucose levels are _____, insulin levels are _____, and glucagon levels _____.
a. high; low; stay the same
b. low; low; stay the same
c. high; high; are high
d. high; high; are low

**20.** Starvation sets in after 3 to 4 days without food. Which hormones change in response to low glucose levels?
a. glucagon and insulin
b. ketones and glucagon
c. insulin, glucose, and glucagon
d. insulin and ketones

**21.** The postabsorptive state relies on stores of _____ in the _____.
a. insulin; pancreas
b. glucagon; pancreas
c. glycogen; liver
d. glucose; liver

**22.** The body's temperature is controlled by the _____. This temperature is always kept between _____.
a. pituitary; 36.5–37.5 °C
b. hypothalamus; 97.7–99.5 °F
c. hypothalamus; 36.5–37.5 °F
d. 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?
a. shivering
b. sweating
c. erection of the hairs on the arms and legs
d. all of the above

**24.** The heat you feel on your chair when you stand up was transferred from your skin via _____.
a. conduction
b. convection
c. radiation
d. evaporation

**25.** A crowded room warms up through the mechanism of _____.
a. conduction
b. convection
c. radiation
d. evaporation

**26.** A deficiency in vitamin A can result in _____.
a. improper bone development
b. scurvy
c. improper eye development or sight
d. all of the above

**27.** Rickets results in improper bone development in children that arises from the malabsorption of calcium and a deficiency in _____.
a. vitamin D
b. vitamin C
c. vitamin $B_{12}$
d. niacin

**28.** Consuming which type of food will help the most with weight loss?
a. fats
b. vegetables
c. lean meats
d. fruits

**29.** Which of the following is stored in the body?
a. thiamine
b. phosphorous
c. folic acid
d. 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.

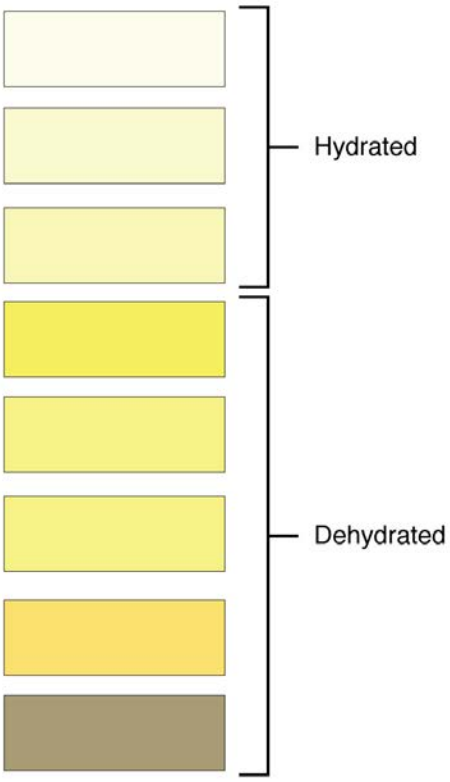



**Figure 25.2 Urine Color**

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 $H_2O$.

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 ($NO_3^-$) occur normally in the urine. Gram-negative bacteria metabolize nitrate into nitrite ($NO_2^-$), 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**).

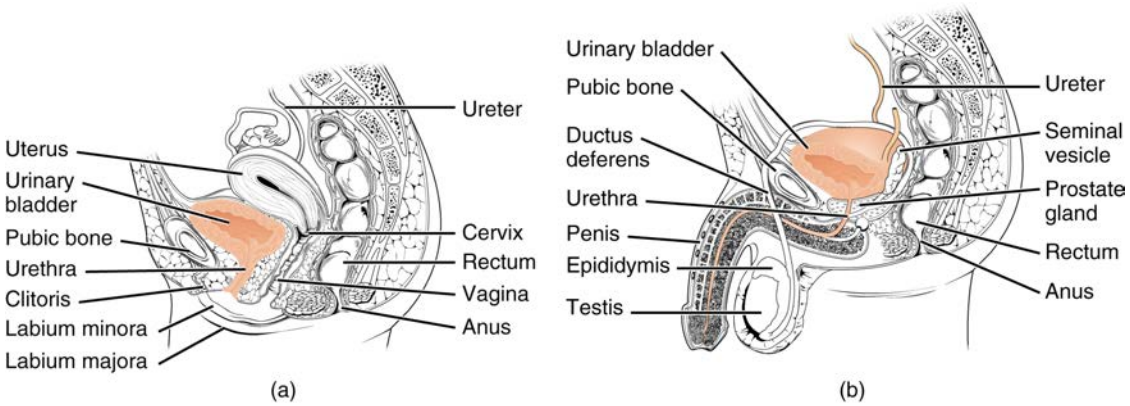



**Figure 25.3 Female and Male Urethras** The urethra transports urine from the bladder to the outside of the body. This image shows (a) a female urethra and (b) a male urethra.

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.

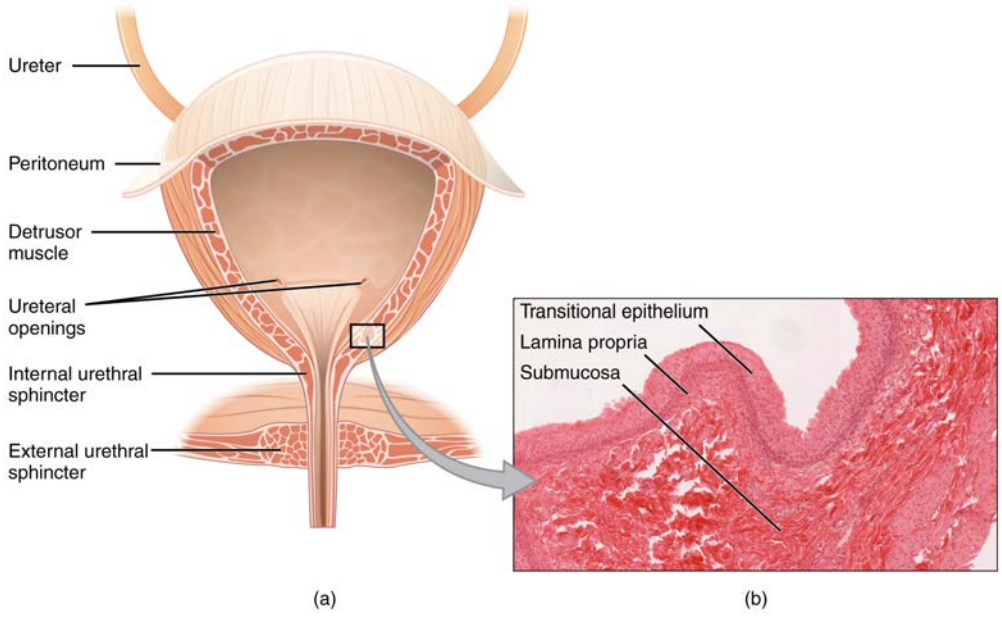



**Figure 25.4 Bladder** (a) Anterior cross section of the bladder. (b) The detrusor muscle of the bladder (source: monkey tissue) LM × 448. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

**Interactive LINK**

View the University of Michigan WebScope at **http://141.214.65.171/Histology/Urinary%20System/212N_HISTO_40X.svs/view.apml (http://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.

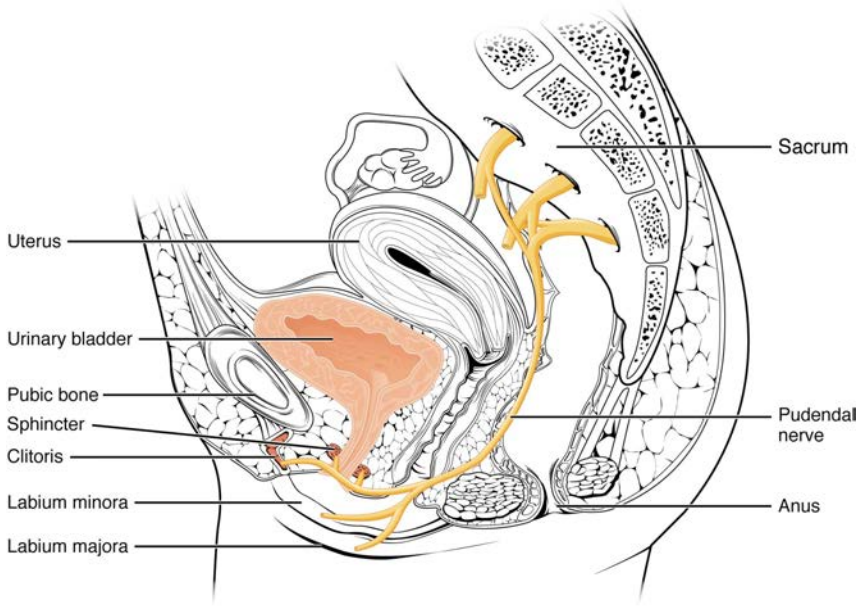



**Figure 25.5 Nerves Innervating the Urinary System**

## 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 hilum 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.

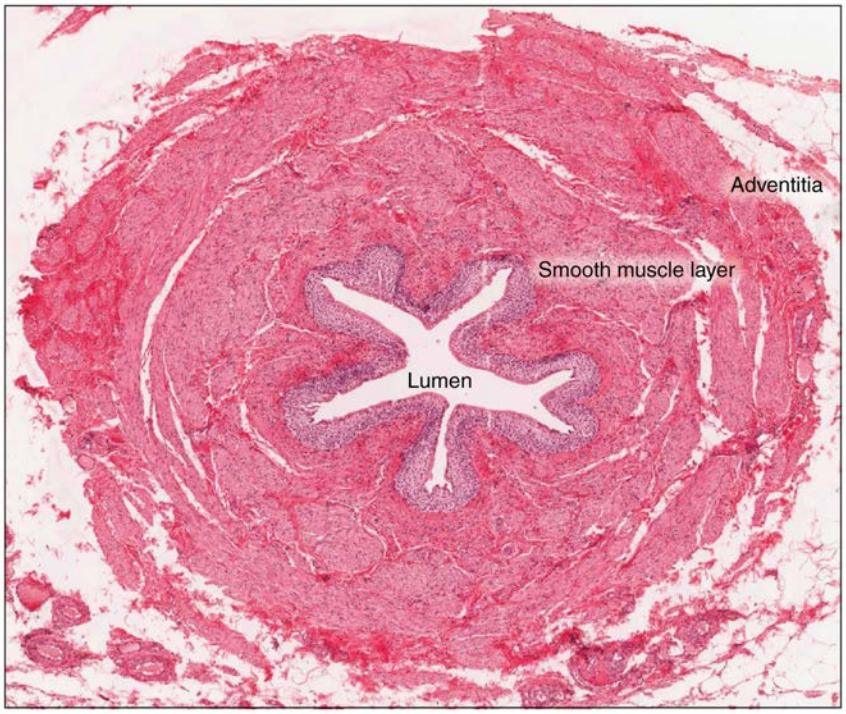



**Figure 25.6 Ureter** Peristaltic contractions help to move urine through the lumen with contributions from fluid pressure and gravity. LM × 128. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

## 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.

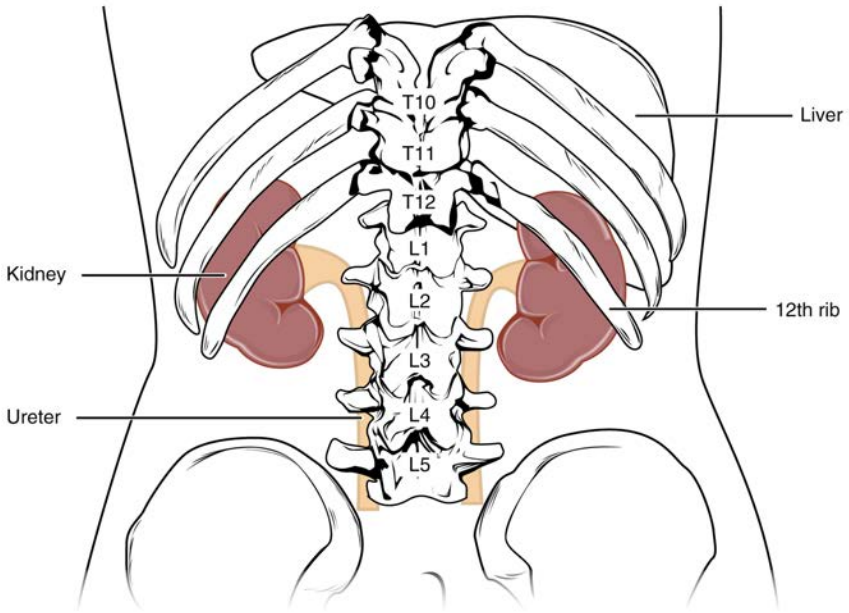



**Figure 25.7 Kidneys** The kidneys are slightly protected by the ribs and are surrounded by fat for protection (not shown).

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.

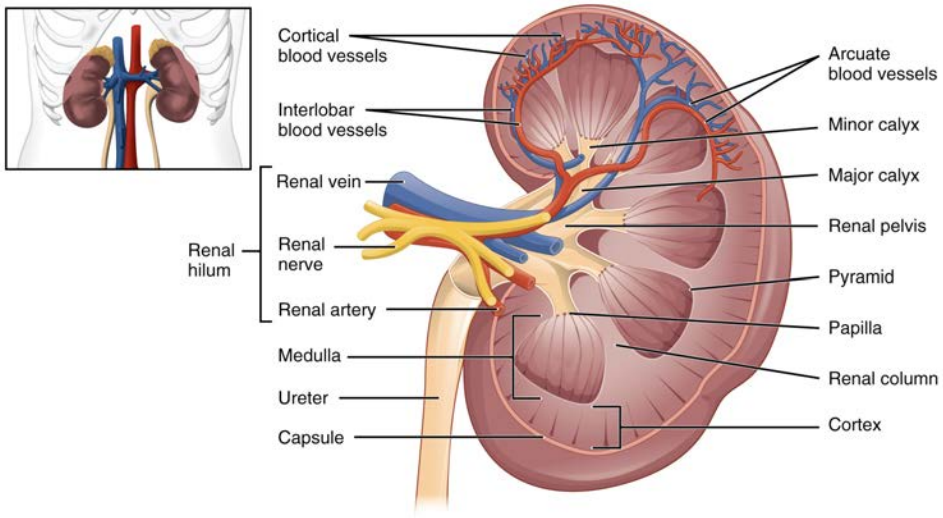



**Figure 25.8 Left Kidney**

## 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 calyxes 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.

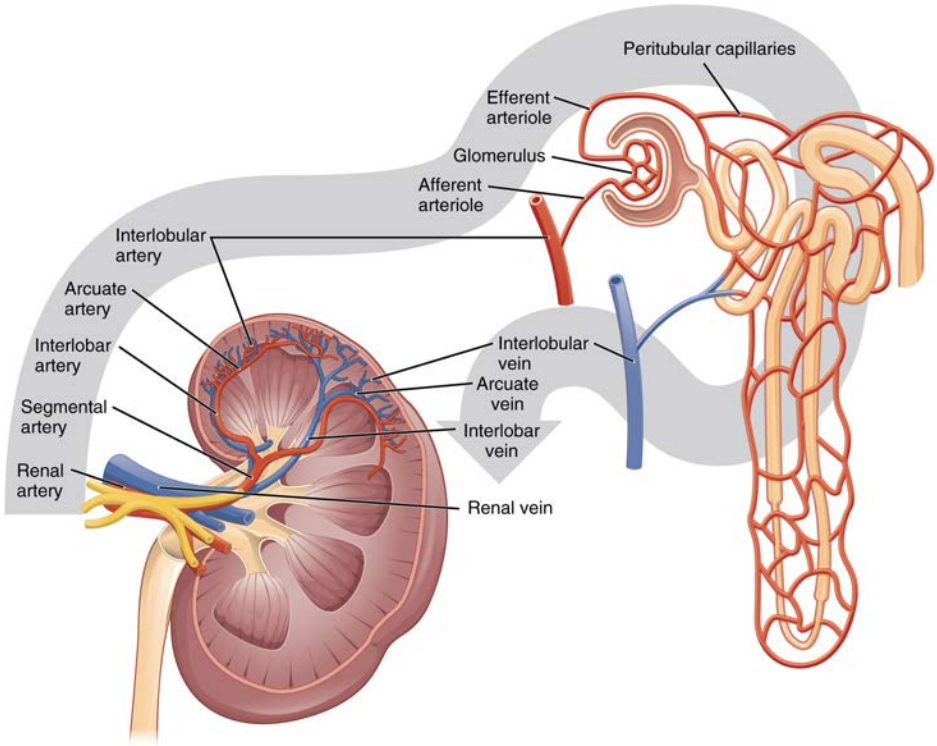



**Figure 25.9 Blood Flow in the Kidney**

**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 µm 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.)

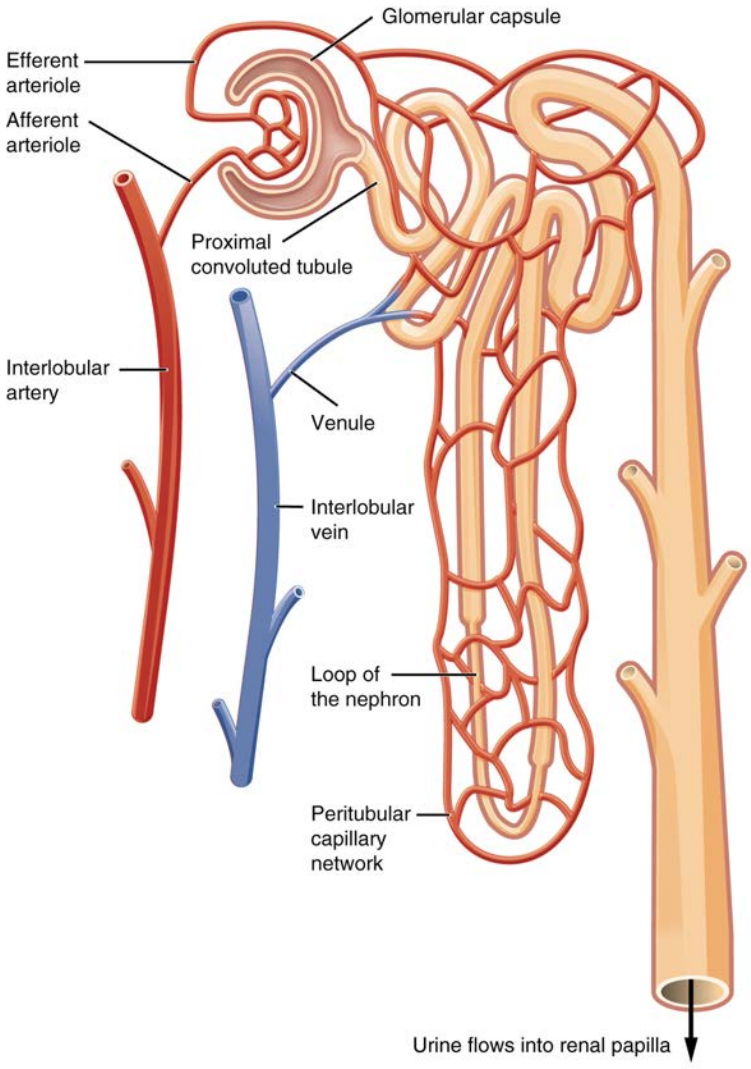



**Figure 25.10 Blood Flow in the Nephron** The two capillary beds are clearly shown in this figure. The efferent arteriole is the connecting vessel between the glomerulus and the peritubular capillaries and vasa recta.

## Interactive LINK

Visit this **link (http://openstaxcollege.org/l/bloodflow5)** 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 though pores that are only 70 nm in diameter.

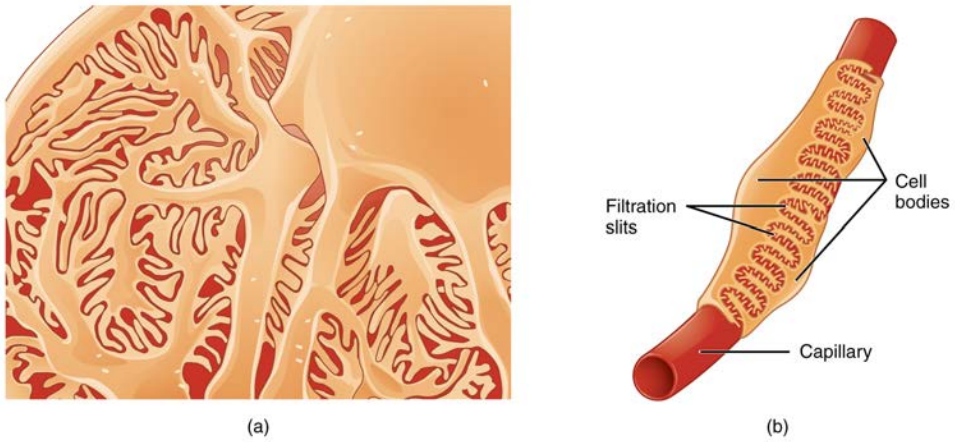



**Figure 25.11 Podocytes** Podocytes interdigitate with structures called pedicels and filter substances in a way similar to fenestrations. In (a), the large cell body can be seen at the top right corner, with branches extending from the cell body. The smallest finger-like extensions are the pedicels. Pedicels on one podocyte always interdigitate with the pedicels of another podocyte. (b) This capillary has three podocytes wrapped around it.

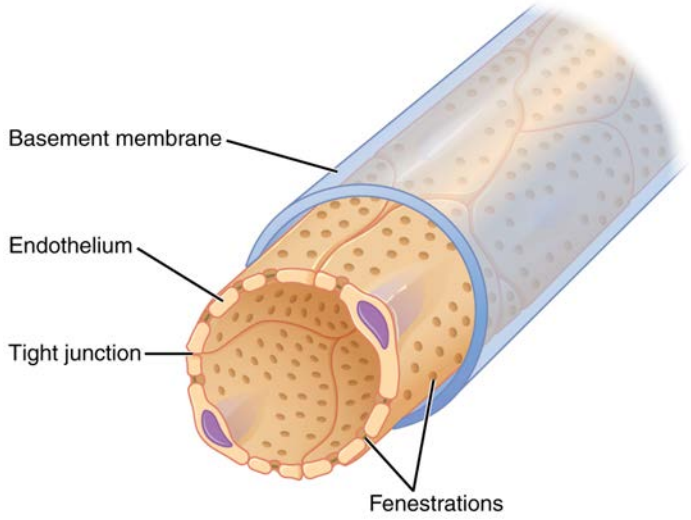



**Figure 25.12 Fenestrated Capillary** Fenestrations allow many substances to diffuse from the blood based primarily on size.

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 $Na^+$ 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 $Na^+$ concentration are adenosine triphosphate (ATP) and adenosine.

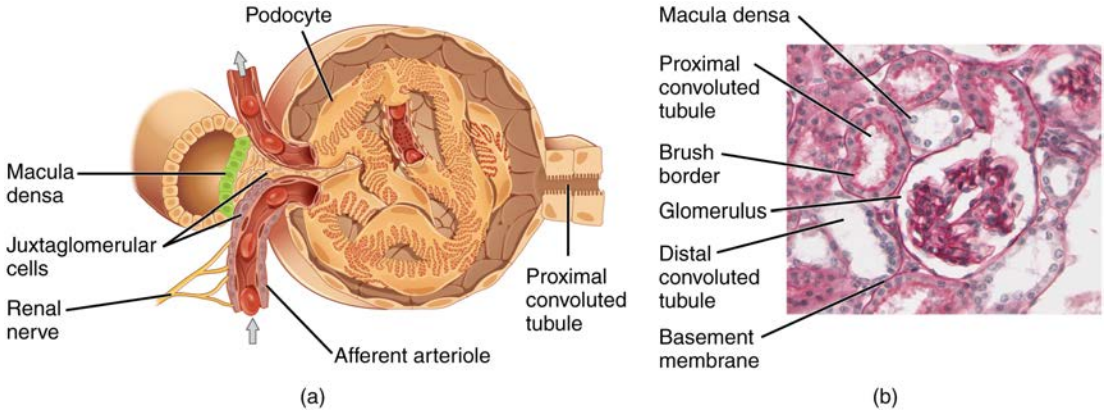



**Figure 25.13 Juxtaglomerular Apparatus and Glomerulus** (a) The JGA allows specialized cells to monitor the composition of the fluid in the DCT and adjust the glomerular filtration rate. (b) This micrograph shows the glomerulus and surrounding structures. LM × 1540. (Micrograph provided by the Regents 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 $Na^+$ reabsorption by the kidney, which also results in water retention and increased blood pressure.

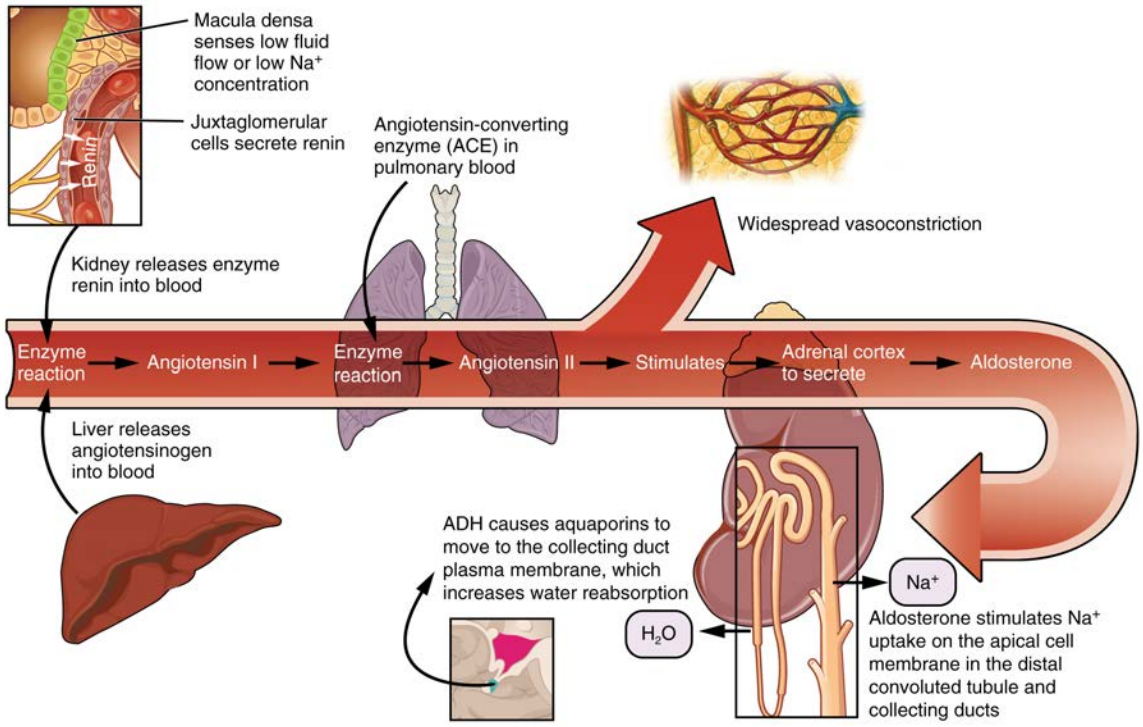



**Figure 25.14 Conversion of Angiotensin I to Angiotensin II** The enzyme renin converts the pro-enzyme angiotensin I; the lung-derived enzyme ACE converts angiotensin I into active angiotensin II.

### 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 ($Na^+$, $Cl^-$, 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 consists 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).

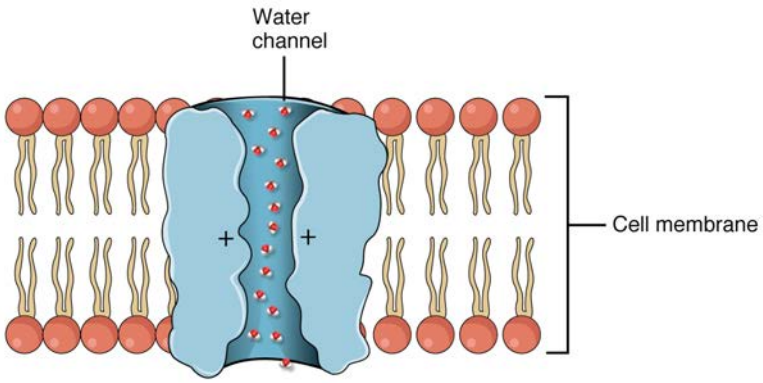



**Figure 25.15 Aquaporin Water Channel** Positive charges inside the channel prevent the leakage of electrolytes across the cell membrane, while allowing water to move due to osmosis.

## 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 |
| Metabolic acidosis |
| Metabolic alkalosis |
| Heart arrhythmias |
| Uremia (high urea level in the blood) |
| Loss of appetite |
| Fatigue |

**Table 25.3**

### Symptoms of Kidney Failure

| |
|---|
| 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.<br><br>5000*0.21 = 1050 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.<br><br>1050*0.55 = 578 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).<br><br>578*0.19 = 110 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).<br><br>110*.08 = 0.9 mL urine /min<br><br>Multiply urine/min times 60 minutes times 24 hours to get daily urine production.<br><br>0.9*60*24 = 1296 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**).

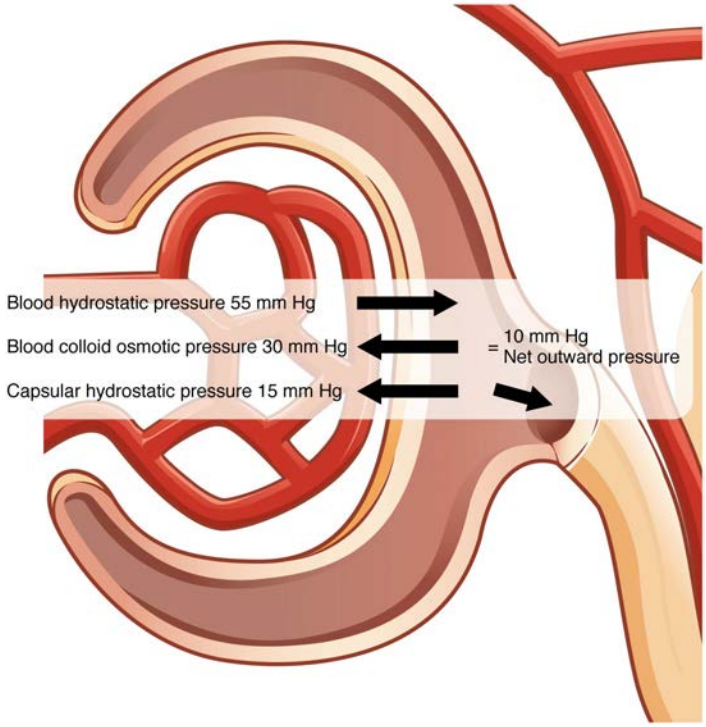



**Figure 25.16 Net Filtration Pressure** The NFP is the sum of osmotic and hydrostatic pressures.

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 = Glomerular blood hydrostatic pressure (GBHP) – [capsular hydrostatic pressure (CHP) + blood colloid osmotic pressure (BCOP)] = 10 mm Hg

That is:

NFP = GBHP – [CHP + BCOP] = 10 mm Hg

Or:

NFP = 55 – [15 + 30] = 10 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.

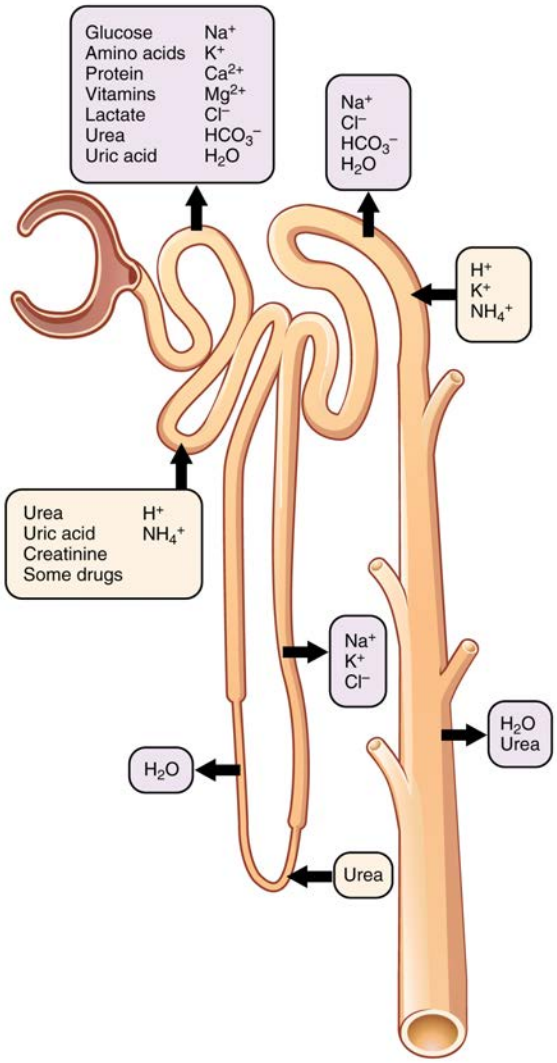



**Figure 25.17 Locations of Secretion and Reabsorption in the Nephron**

## 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 $Na^+$ | | | |
| Oligopeptides, proteins, amino acids | Almost 100 percent reabsorbed; symport with $Na^+$ | | | |
| Vitamins | Reabsorbed | | | |
| Lactate | Reabsorbed | | | |
| Creatinine | Secreted | | | |
| Urea | 50 percent reabsorbed by diffusion; also secreted | Secretion, diffusion in descending limb | | Reabsorption in medullary collecting ducts; diffusion |

**Table 25.5**

### Substances Secreted or Reabsorbed in the Nephron and Their Locations

| Substance | PCT | Loop of Henle | DCT | Collecting ducts |
|---|---|---|---|---|
| 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 $Na^+$, 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 $Na^+$ | Reabsorbed, symport with $Na^+$ and antiport with $Cl^–$; in ascending limb | | Reabsorbed antiport with $Cl^–$ |
| $H^+$ | Secreted; diffusion | | Secreted; active | Secreted; active |
| $NH_4^+$ | Secreted; diffusion | | Secreted; diffusion | Secreted; diffusion |
| $HCO_3^–$ | Reabsorbed; diffusion | Reabsorbed; diffusion in ascending limb | Reabsorbed; diffusion | Reabsorbed; antiport with $Na^+$ |
| 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 $Na^+$ out of a cell and $K^+$ into a cell by the $Na^+/K^+$ 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, $Na^+$ ions, is an example of facilitated diffusion. In some cases of facilitated diffusion, 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. This is a mechanism described by the term "secondary active transport." For example, a $Na^+$ ATPase pump on the basilar membrane of a cell may constantly pump $Na^+$ out of a cell, maintaining a strong electrochemical gradient. On the opposite (apical) surface, a $Na^+$/glucose symport protein channel assists both $Na^+$ and glucose into the cell as $Na^+$ moves down the concentration gradient created by the basilar $Na^+$ ATPase pumps. 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 $Ca^{++}$, $Na^+$, glucose, and amino acids must be reabsorbed by the nephron to maintain homeostatic plasma concentrations. Other substances, such as urea, $K^+$, ammonia ($NH_3$), 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 $H^+$, whereas the kidneys secrete or reabsorb $H^+$ and $HCO_3^-$ (**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 $Na^+$ (**Figure 25.18**).

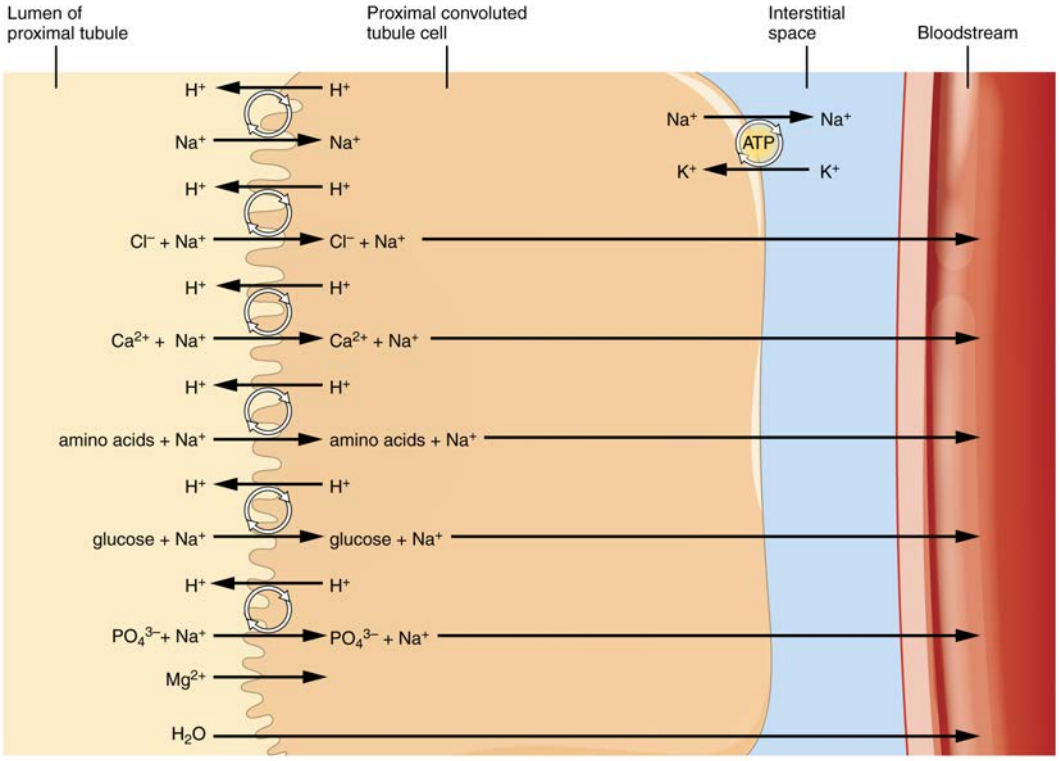



**Figure 25.18 Substances Reabsorbed and Secreted by the PCT**

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 $Na^+$. 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 (**Table 25.7**). A few of the substances that are transported with $Na^+$ (symport mechanism) on the apical membrane include $Cl^-$, $Ca^{++}$, amino acids, glucose, and $PO_4^{3-}$. Sodium is actively exchanged for $K^+$ 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, $K^+$, $Ca^{++}$, and $Mg^{++}$, diffuse laterally between adjacent cell membranes (transcellular).

## Reabsorption of Major Solutes by the PCT

| Basal membrane | Apical membrane |
|---|---|
| Active transport | Symport with $Na^+$ |
| $Na^+$ (exchange for $K^+$) | $K^+$ |
| Facilitated diffusion | $Cl^-$ |
| $K^+$ | $Ca^{++}$ |
| $Cl^-$ | $Mg^{++}$ |
| $Ca^{++}$ | $HCO_3^-$ |
| $HCO_3^-$ | $PO_4^{3-}$ |

**Table 25.7**

## Reabsorption of Major Solutes by the PCT

| Basal membrane | Apical membrane |
|---|---|
| $PO_4^{3-}$ | Amino acids |
| Amino acids | Glucose |
| Glucose | Fructose |
| Fructose | Galactose |
| Galactose | Lactate |
| Lactate | Succinate |
| Succinate | Citrate |
| Citrate | Diffusion between nephron cells |
| | $K^+$ |
| | $Ca^{++}$ |
| | $Mg^{++}$ |

**Table 25.7**

About 67 percent of the water, $Na^+$, and $K^+$ 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 $Na^+$ 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. $Na^+$ 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 $Na^+/K^+$ ATPase that pumps $Na^+$ out of the cell on the basal surface. Fifty percent of $Cl^-$ and variable quantities of $Ca^{++}$, $Mg^{++}$, and $HPO_4^{2-}$ are also recovered in the PCT.

Recovery of bicarbonate ($HCO_3^-$) 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 $CO_2$, in the stomach to produce hydrochloric acid, and in the pancreas to produce $HCO_3^-$ 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, $HCO_3^-$ combines with hydrogen ions to form carbonic acid ($H_2CO_3$). This is enzymatically catalyzed into $CO_2$ 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 ($HCO_3^-$). These bicarbonate ions are cotransported with $Na^+$ across the basal membrane to the interstitial space around the PCT (**Figure 25.19**). At the same time this is occurring, a $Na^+/H^+$ antiporter excretes $H^+$ into the lumen, while it recovers $Na^+$. Note how the hydrogen ion is recycled so that bicarbonate can be recovered. Also, note that a $Na^+$ gradient is created by the $Na^+/K^+$ pump.

$$HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

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.

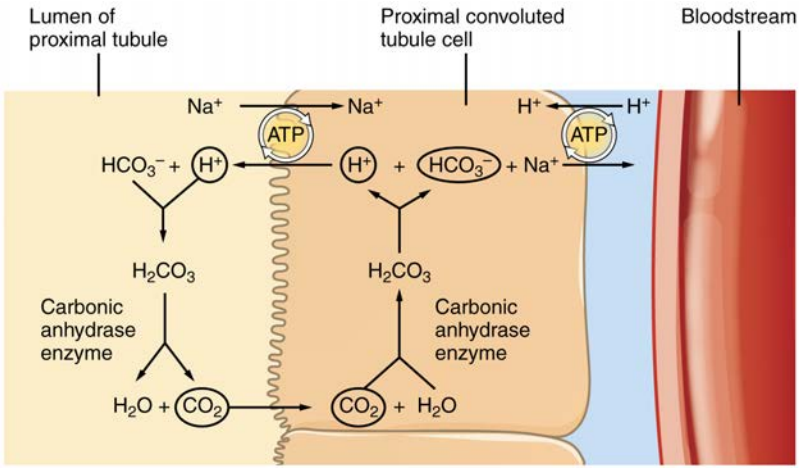



**Figure 25.19 Reabsorption of Bicarbonate from the PCT**

## 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 $Na^+$ 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, $Na^+$, 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 $Na^+$, are actively pumped out of the loop by large quantities of the $Na^{+}/K^+$ ATPase pump. This has two significant effects: Removal of $Na^+$ while retaining water leads to a hypotonic filtrate by the time it reaches the DCT; pumping $Na^+$ into the interstitial space contributes to the hyperosmotic environment in the kidney medulla.

The $Na^{+}/K^+$ ATPase pumps in the basal membrane create an electrochemical gradient, allowing reabsorption of $Cl^–$ by $Na^{+}/Cl^–$ symporters in the apical membrane. At the same time that $Na^+$ is actively pumped from the basal side of the cell into the interstitial fluid, $Cl^–$ follows the $Na^+$ 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 $K^+$ 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” $K^+$, there is one $Na^+$ and two $Cl^–$ 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 ($Na^+$, $K^+$, $Ca^{++}$, and $Mg^{++}$) 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 $Na^+$ deep in the medulla.

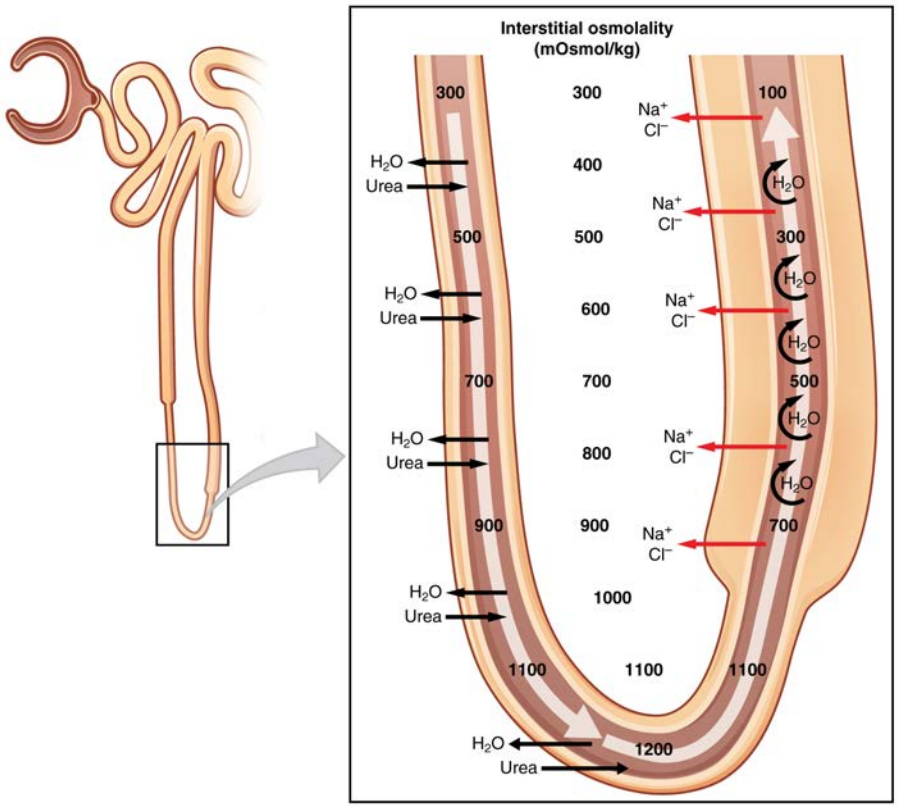



**Figure 25.20 Countercurrent Multiplier System**

As discussed above, the ascending loop has many $Na^+$ pumps that actively pump $Na^+$ 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 $Na^+$ to the circulation via the vasa recta and creates a high osmolar environment in the depths of the medulla.

Ammonia ($NH_3$) is a toxic byproduct of protein metabolism. It is formed as amino acids are deaminated by liver hepatocytes. That means that the amine group, $NH_2$, 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 $Na^+$ 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 $Na^+$ in the circulation.

The amino acid glutamine can be deaminated by the kidney. As $NH_2$ from the amino acid is converted into $NH_3$ and pumped into the lumen of the PCT, $Na^+$ and $HCO_3^-$ 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 $NH_4^+$) in the urine and a gain of a bicarbonate ion ($HCO_3^-$) 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 $Na^+$ from the cell. A $Na^+/K^+/2Cl^-$ 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 $Na^+$ 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, $Na^+$ and urea are freely able to enter the capillary, while water freely leaves; as they ascend, $Na^+$ and urea are secreted into the surrounding medulla, while water reenters and is removed.

**Interactive LINK**


Watch this **video (http://openstaxcollege.org/l/multiplier)** 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 $Na^+/K^+$ ATPase in the basal membrane of the DCT and collecting duct. The movement of $Na^+$ out of the lumen of the collecting duct creates a negative charge that promotes the movement of $Cl^-$ 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 $Ca^{++}$ 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 $Ca^{++}$ recovery from the forming urine. In addition, as $Na^+$ is pumped out of the cell, the resulting electrochemical gradient attracts $Ca^{++}$ 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 $Ca^{++}$ 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 $Ca^{++}$ 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 $Na^+$ 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 $Na^+$ recovery. Aldosterone stimulates principal cells to manufacture luminal $Na^+$ and $K^+$ channels as well as $Na^+/K^+$ ATPase pumps on the basal membrane of the cells. When aldosterone output increases, more $Na^+$ is recovered from the forming urine and water follows the $Na^+$ passively. As the pump recovers $Na^+$ for the body, it is also pumping $K^+$ into the forming urine, since the pump moves $K^+$ in the opposite direction. When aldosterone decreases, more $Na^+$ remains in the forming urine and more $K^+$ is recovered in the circulation. Symport channels move $Na^+$ and $Cl^-$ together. Still other channels in the principal cells secrete $K^+$ into the collecting duct in direct proportion to the recovery of $Na^+$.

Intercalated cells play significant roles in regulating blood pH. Intercalated cells reabsorb $K^+$ and $HCO_3^-$ while secreting $H^+$. 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 $Na^+$ 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 25.8). 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 $Na^+$ concentration. As GFR increases, there is less time for 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 $Na^+$ 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 vasoconstricton | Vasoconstriction decreases GFR |

Table 25.8

# 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 biologic 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 $Ca^{++}$ 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 ($PO_3^-$), causing its loss in the urine. The retention of phosphate would result in the formation of calcium phosphate in the plasma, reducing circulating $Ca^{++}$ levels. By ridding the blood of phosphate, higher circulating $Ca^{++}$ levels are permitted.

| | Stimulus | Effect on GFR | Effect on RBF |
|---|---|---|---|
| **VASOCONSTRICTORS** | | | |
| Sympathetic nerves (epinephrine and norepinephrine) | ↓ ECFV | ↓ | ↓ |
| Angiotensin II | ↓ ECFV | ↓ | ↓ |
| Endothelin | ↑ Stretch, bradykinin, angiotensin II, epinephrine<br>↓ ECFV | ↓ | ↓ |
| **VASODILATORS** | | | |
| Prostaglandins (PGE1, PGE2, and PGI2) | ↓ ECFV<br>↑ shear stress, angiotensin II | No change/↑ | ↑ |
| Nitric oxide (NO) | ↑ shear stress, acetylcholine, histamine, bradykinin, ATP, adenosine | ↑ | ↑ |
| Bradykinin | Prostaglandins,<br>↓ 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 RFB**

# 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 $Na^+$ 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 $Na^+$ 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 $Na^+$ by the DCT and collecting ducts. More $Na^+$ 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 $Na^+$/ $Cl^-$ symporter in the DCT and collecting duct. The result is a loss of $Na^+$ 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 $Na^+$

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 $Na^+$ 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 $Na^+$ concentration include the renin–angiotensin–aldosterone system and ADH (see **Figure 25.14**). Aldosterone stimulates the uptake of $Na^+$ on the apical cell membrane of cells in the DCT and collecting ducts, whereas ADH helps to regulate $Na^+$ concentration indirectly by regulating the reabsorption of water.

## Regulation of Extracellular $K^+$

Potassium is present in a 30-fold greater concentration inside the cell than outside the cell. A generalization can be made that $K^+$ and $Na^+$ concentrations will move in opposite directions. When more $Na^+$ is reabsorbed, more $K^+$ is secreted; when less $Na^+$ is reabsorbed (leading to excretion by the kidney), more $K^+$ is retained. When aldosterone causes a recovery of $Na^+$ in the nephron, a negative electrical gradient is created that promotes the secretion of $K^+$ and $Cl^-$ into the lumen.

## Regulation of $Cl^-$

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 $Na^+$ in the extracellular environment makes it the dominant anion of this compartment, and its regulation closely mirrors that of $Na^+$.

## Regulation of $Ca^{++}$ and Phosphate

The parathyroid glands monitor and respond to circulating levels of $Ca^{++}$ in the blood. When levels drop too low, PTH is released to stimulate the DCT to reabsorb $Ca^{++}$ from the forming urine. When levels are adequate or high, less PTH is released and more $Ca^{++}$ remains in the forming urine to be lost. Phosphate levels move in the opposite direction. When $Ca^{++}$ levels are low, PTH inhibits reabsorption of $HPO_4^{2-}$ so that its blood level drops, allowing $Ca^{++}$ 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 $Ca^{++}$ from the diet.

## Regulation of $H^+$, 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, $HCO_3^{2-}$, and ammonia have a very large capacity to absorb or release $H^+$ 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 $HCO_3^-$ into $CO_2$, 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 $H^+$ into the forming urine as $Na^+$ is reabsorbed. The body rids itself of excess $H^+$ and raises blood pH. In the collecting ducts, the apical surfaces of intercalated cells have proton pumps that actively secrete $H^+$ 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 ($HCO_3^-$), $H_2PO_4^-$ (dihydrogen phosphate ion), or ammonia (forming $NH_4^+$, 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 ($NH_2$) groups into ammonia ($NH_3$), ammonium ion ($NH_4^+$), 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.

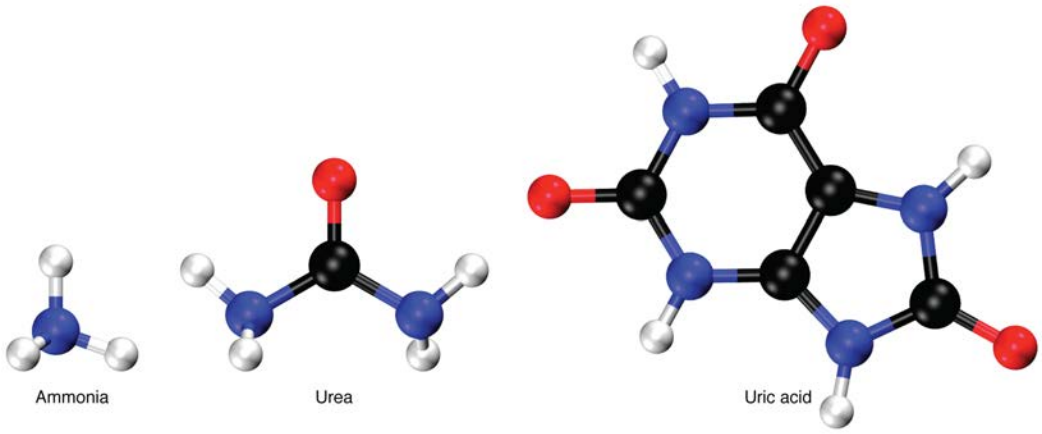



**Figure 25.22 Nitrogen Wastes**

## 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 dieresis 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 $Na^{+}$ and its associated osmotic recovery of water. The reabsorption of $Na^{+}$ helps to raise and maintain blood pressure over a longer term.

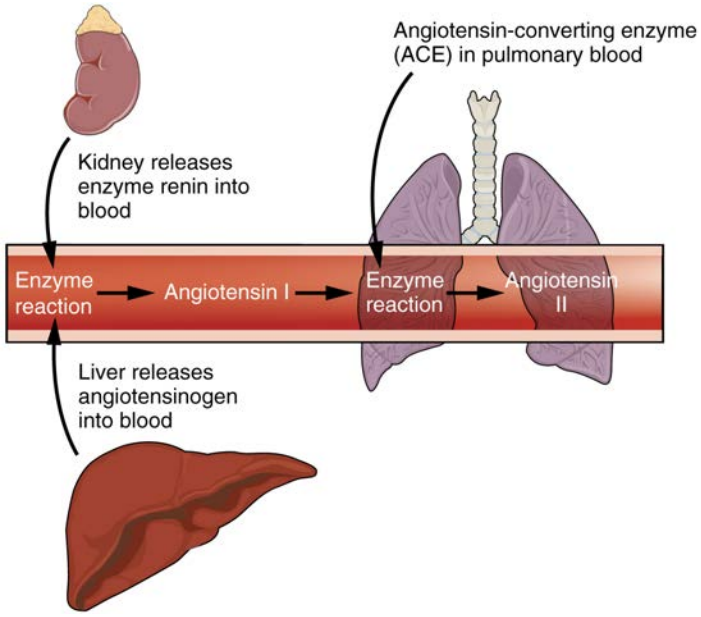



**Figure 25.23 The Enzyme Renin Converts the Pro-enzyme Angiotensin**

## 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 $Na^+$ and $Ca^{++}$ homeostasis has been discussed at length. Failure of $K^+$ 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 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 I** protein produced by the enzymatic action of renin on angiotensinogen; inactive precursor of angiotensin II

**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 $Na^+$ 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 $Na^+$ 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, $NH_3$, creatinine, and some drugs are filtered or secreted as wastes. $H^+$ and $HCO_3^-$ 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 ($HCO_3^-$) 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 juxtaglomerular 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 $Na^+$, reducing filtrate osmolarity to 50–100 mOsmol/kg. The descending and ascending loop and vasa recta form a countercurrent multiplier system to increase $Na^+$ 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 $Na^+$ 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 $Na^+$, 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 $Na^+$ retention and decreasing GFR. Natriuretic hormones, released primarily from the atria of the heart in response to stretching of the atrial walls, stimulate $Na^+$ 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 $Ca^{++}$ 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 $Na^+$ 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 $Na^+$ concentration in the blood include the renin–angiotensin–aldosterone system and ADH. When $Na^+$ is retained, $K^+$ is excreted; when $Na^+$ is lost, $K^+$ is retained. When circulating $Ca^{++}$ decreases, PTH stimulates the reabsorption of $Ca^{++}$ and inhibits reabsorption of $HPO_4^{2-}$. pH is regulated through buffers, expiration of $CO_2$, 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 $Ca^{++}$. The kidney hormone EPO stimulates erythrocyte development and promotes adequate $O_2$ transport. The kidneys help regulate blood pressure through $Na^+$ 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: $Na^+$, $Ca^{++}$, and $K^+$. 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

**1.** Diabetes insipidus or diabetes mellitus would most likely be indicated by _____.
- a. anuria
- b. polyuria
- c. oliguria
- d. none of the above

**2.** The color of urine is determined mainly by _____.
- a. diet
- b. filtration rate
- c. byproducts of red blood cell breakdown
- d. filtration efficiency

**3.** Production of less than 50 mL/day of urine is called _____.
- a. normal
- b. polyuria
- c. oliguria
- d. anuria

**4.** Peristaltic contractions occur in the _____.
- a. urethra
- b. bladder
- c. ureters
- d. urethra, bladder, and ureters

**5.** Somatic motor neurons must be _____ to relax the external urethral sphincter to allow urination.
- a. stimulated
- b. inhibited

**6.** Which part of the urinary system is *not* completely retroperitoneal?
- a. kidneys
- b. ureters
- c. bladder
- d. nephrons

**7.** The renal pyramids are separated from each other by extensions of the renal cortex called _____.
- a. renal medulla
- b. minor calyces
- c. medullary cortices
- d. renal columns

**8.** The primary structure found within the medulla is the _____.
- a. loop of Henle
- b. minor calyces
- c. portal system
- d. ureter

**9.** The right kidney is slightly lower because _____.
- a. it is displaced by the liver
- b. it is displace by the heart
- c. it is slightly smaller
- d. it needs protection of the lower ribs

**10.** Blood filtrate is captured in the lumen of the _____.
- a. glomerulus
- b. Bowman's capsule
- c. calyces
- d. renal papillae

**11.** What are the names of the capillaries following the efferent arteriole?
- a. arcuate and medullary
- b. interlobar and interlobular
- c. peritubular and vasa recta
- d. peritubular and medullary

**12.** The functional unit of the kidney is called _____.
- a. the renal hilus
- b. the renal corpuscle
- c. the nephron
- d. Bowman's capsule

**13.** _____ pressure must be greater on the capillary side of the filtration membrane to achieve filtration.
- a. Osmotic
- b. Hydrostatic

**14.** Production of urine to modify plasma makeup is the result of _____.
- a. filtration
- b. absorption
- c. secretion
- d. filtration, absorption, and secretion

**15.** Systemic blood pressure must stay above 60 so that the proper amount of filtration occurs.
- a. true
- b. false

**16.** Aquaporin channels are only found in the collecting duct.

a. true
b. false

**17.** Most absorption and secretion occurs in this part of the nephron.
a. proximal convoluted tubule
b. descending loop of Henle
c. ascending loop of Henle
d. distal convoluted tubule
e. collecting ducts

**18.** The fine tuning of water recovery or disposal occurs in _____.
a. the proximal convoluted tubule
b. the collecting ducts
c. the ascending loop of Henle
d. the distal convoluted tubule

**19.** Vasodilation of blood vessels to the kidneys is due to _____.
a. more frequent action potentials
b. less frequent action potentials

**20.** When blood pressure increases, blood vessels supplying the kidney will _____ to mount a steady rate of filtration.
a. contract
b. relax

**21.** Which of these three paracrine chemicals cause vasodilation?
a. ATP
b. adenosine
c. nitric oxide

**22.** What hormone directly opposes the actions of natriuretic hormones?
a. renin
b. nitric oxide
c. dopamine
d. aldosterone

**23.** Which of these is a vasoconstrictor?
a. nitric oxide
b. natriuretic hormone
c. bradykinin
d. angiotensin II

**24.** What signal causes the heart to secrete atrial natriuretic hormone?
a. increased blood pressure
b. decreased blood pressure
c. increased $Na^+$ levels
d. decreased $Na^+$ levels

**25.** Which of these beverages does *not* have a diuretic effect?
a. tea
b. coffee
c. alcohol
d. milk

**26.** Progesterone can bind to receptors for which hormone that, when released, activates water retention?
a. aldosterone
b. ADH
c. PTH
d. ANH

**27.** Renin is released in response to _____.
a. increased blood pressure
b. decreased blood pressure
c. ACE
d. diuretics

**28.** Which step in vitamin D production does the kidney perform?
a. converts cholecalciferol into calcidiol
b. converts calcidiol into calcitriol
c. stores vitamin D
d. none of these

**29.** Which hormone does the kidney produce that stimulates red blood cell production?
a. thrombopoeitin
b. vitamin D
c. EPO
d. renin

**30.** If there were no aquaporin channels in the collecting duct, _____.
a. you would develop systemic edema
b. you would retain excess $Na^+$
c. you would lose vitamins and electrolytes
d. you would suffer severe dehydration

## CRITICAL THINKING QUESTIONS

**31.** What is suggested by the presence of white blood cells found in the urine?

**32.** Both diabetes mellitus and diabetes insipidus produce large urine volumes, but how would other characteristics of the urine differ between the two diseases?

**33.** Why are females more likely to contract bladder infections than males?

**34.** Describe how forceful urination is accomplished.

**35.** What anatomical structures provide protection to the kidney?

**36.** How does the renal portal system differ from the hypothalamo–hypophyseal and digestive portal systems?

**37.** Name the structures found in the renal hilum.

**38.** Which structures make up the renal corpuscle?

**39.** What are the major structures comprising the filtration membrane?

**40.** Give the formula for net filtration pressure.

**41.** Name at least five symptoms of kidney failure.

**42.** Which vessels and what part of the nephron are involved in countercurrent multiplication?

**43.** 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.

**44.** Explain what happens to $Na^+$ concentration in the nephron when GFR increases.

**45.** If you want the kidney to excrete more $Na^+$ in the urine, what do you want the blood flow to do?

**46.** What organs produce which hormones or enzymes in the renin–angiotensin system?

**47.** PTH affects absorption and reabsorption of what?

**48.** Why is ADH also called vasopressin?

**49.** How can glucose be a diuretic?

**50.** How does lack of protein in the blood cause edema?

**51.** 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 narrows 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 and electrolyte. For instance, sodium ions ($Na^+$) and chloride ions ($Cl^-$) 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.

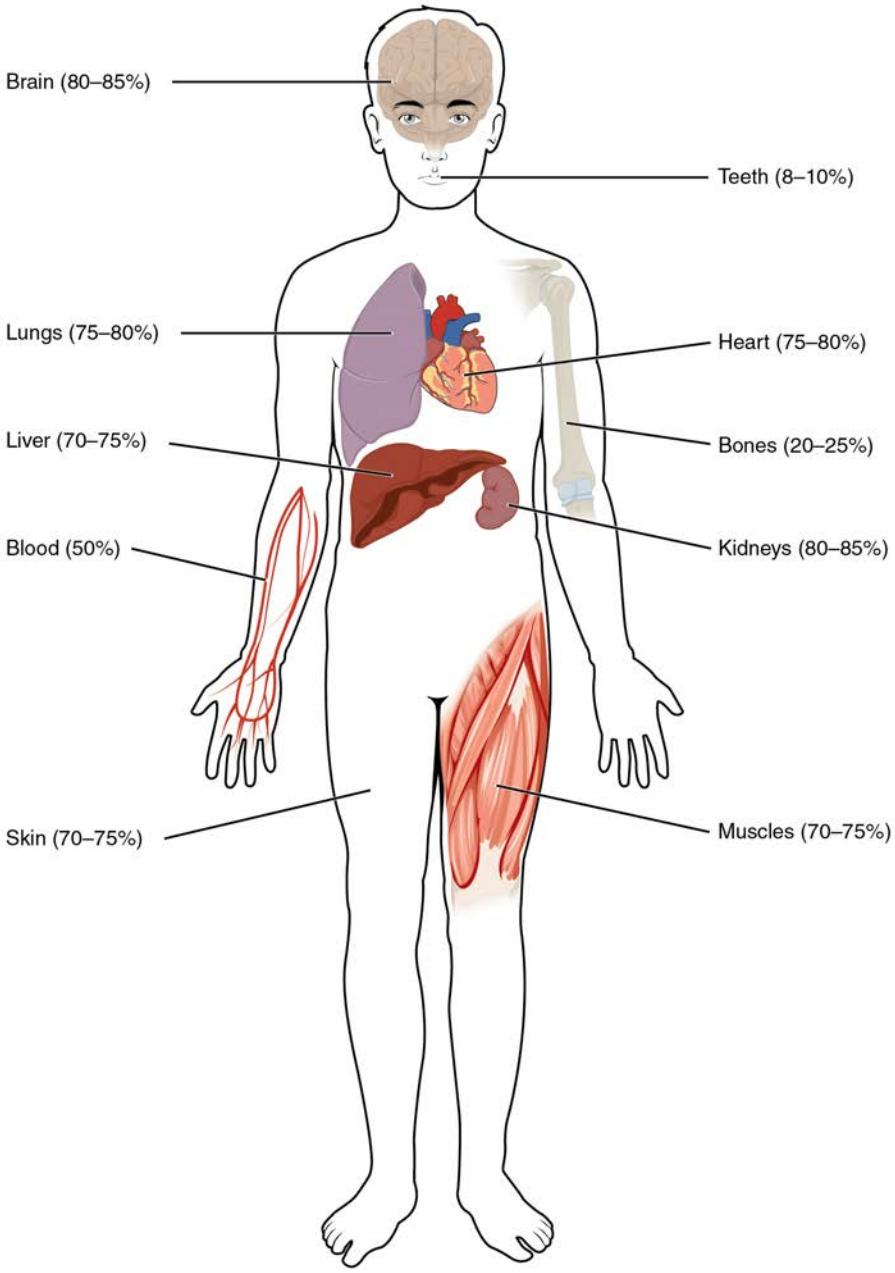



**Figure 26.2 Water Content of the Body's Organs and Tissues** Water content varies in different body organs and tissues, from as little as 8 percent in the teeth to as much as 85 percent in the brain.

## 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**).

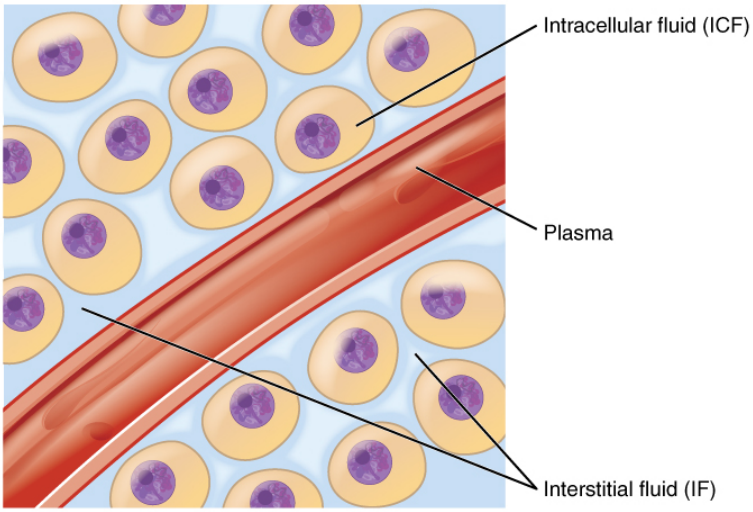



**Figure 26.3 Fluid Compartments in the Human Body** The intracellular fluid (ICF) is the fluid within cells. The interstitial fluid (IF) is part of the extracellular fluid (ECF) between the cells. Blood plasma is the second part of the ECF. Materials travel between cells and the plasma in capillaries 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.

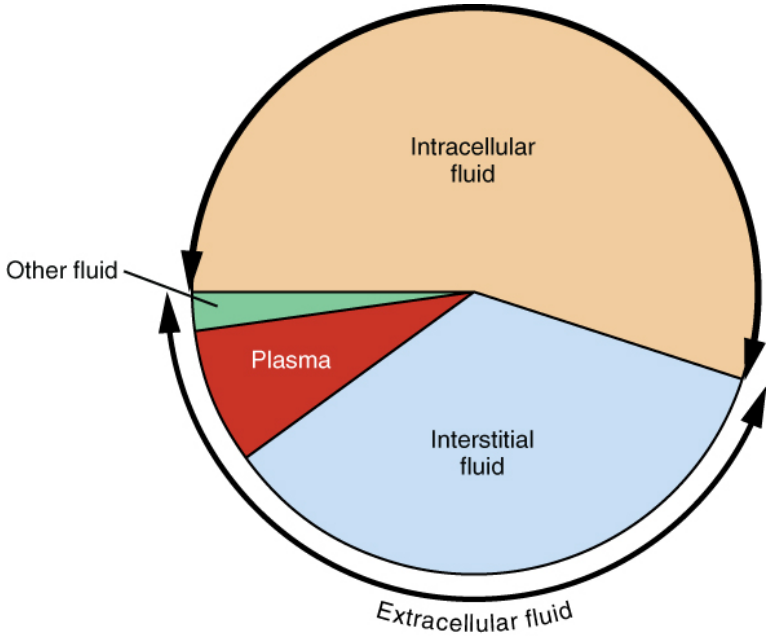



**Figure 26.4 A Pie Graph Showing the Proportion of Total Body Fluid in Each of the Body's Fluid Compartments** Most of the water in the body is intracellular fluid. The second largest volume is the interstitial fluid, which surrounds cells that are not blood cells.

## 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 ( $HPO_4^{2-}$ ), whereas both plasma and the ECF contain high concentrations of sodium and chloride.

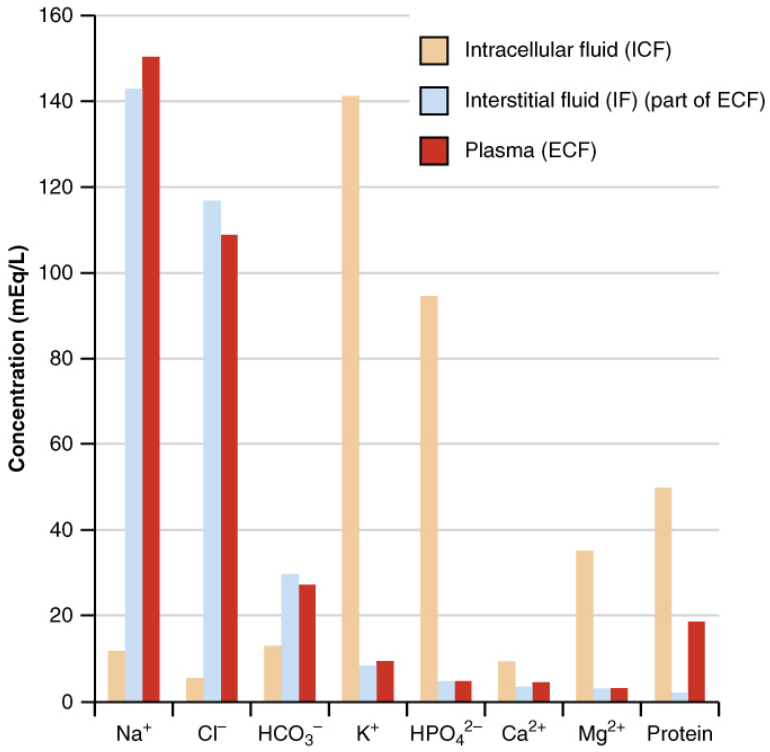



**Figure 26.5 The Concentrations of Different Elements in Key Bodily Fluids** The graph shows the composition of the ICF, IF, and plasma. The compositions of plasma and IF are similar to one another but are quite different from the composition of the ICF.

**Interactive LINK**

Watch this **video (http://openstaxcollege.org/l/bodyfluids)** 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 ($Na^+$) ions and chloride ($Cl^-$) ions are concentrated in

the ECF of the body, whereas potassium ($K^+$) 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**).

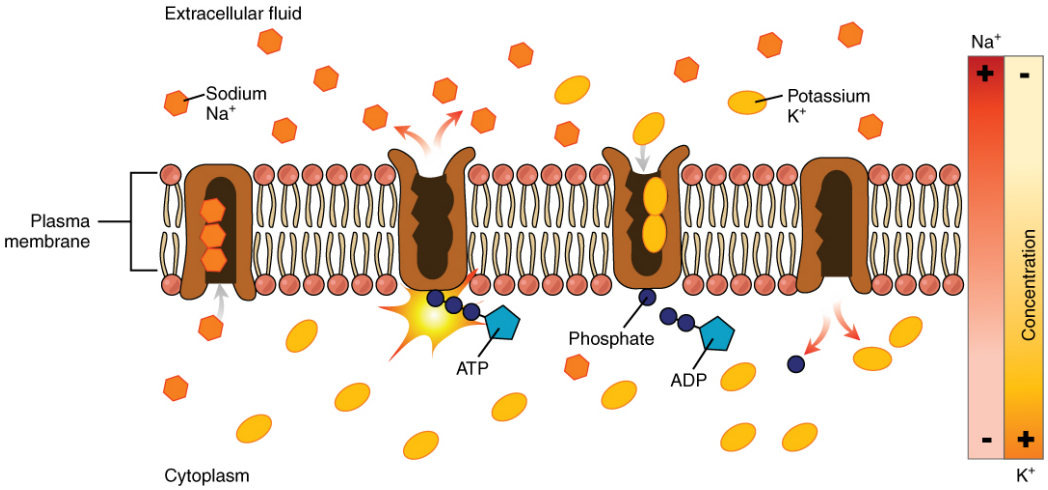



**Figure 26.6 The Sodium-Potassium Pump** The sodium-potassium pump is powered by ATP to transfer sodium out of the cytoplasm and into the ECF. The pump also transfers potassium out of the ECF and into the cytoplasm. (credit: modification of work by Mariana Ruiz Villarreal)

## 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.

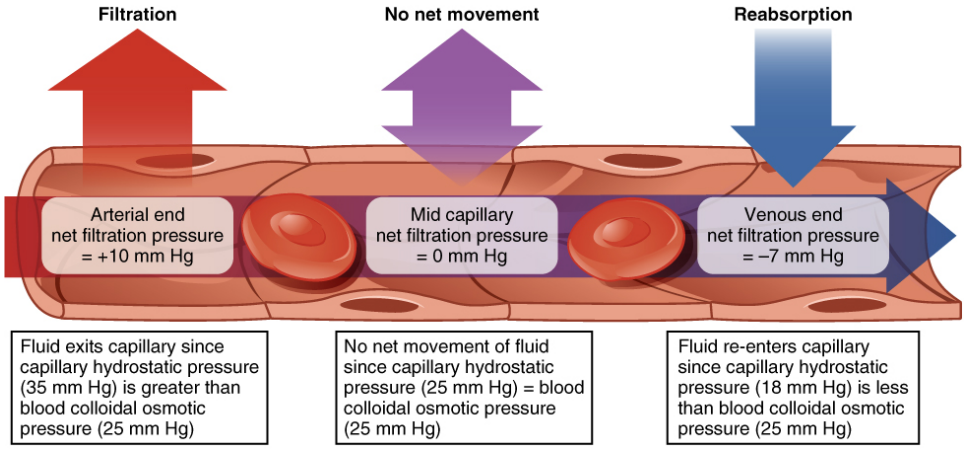



**Figure 26.7 Capillary Exchange** Net filtration occurs near the arterial end of the capillary since capillary hydrostatic pressure (CHP) is greater than blood colloidal osmotic pressure (BCOP). There is no net movement of fluid near the midpoint of the capillary since CHP = BCOP. Net reabsorption occurs near the venous end of the capillary since BCOP is greater than CHP.

**Interactive LINK**

Watch this **video (http://openstaxcollege.org/l/dynamicfluid)** 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**).

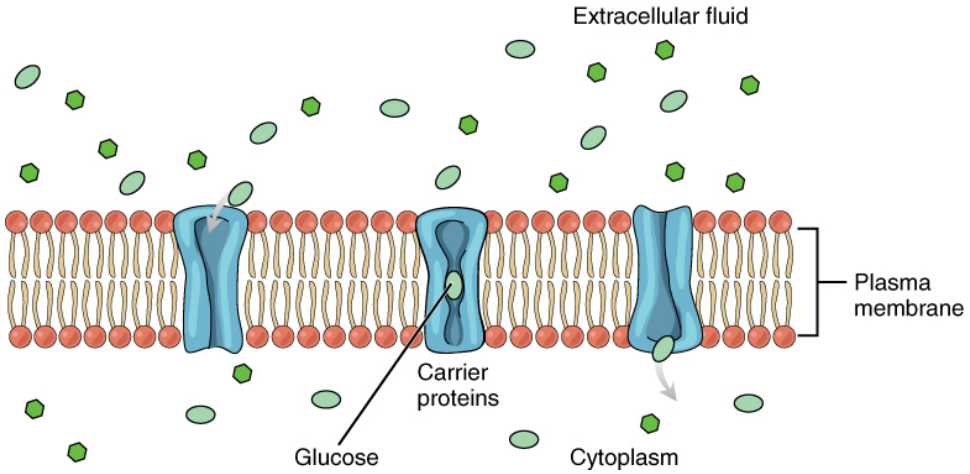



**Figure 26.8 Facilitated Diffusion** Glucose molecules use facilitated diffusion to move down a concentration gradient through the carrier protein channels in the membrane. (credit: modification of work by Mariana Ruiz Villarreal)

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.

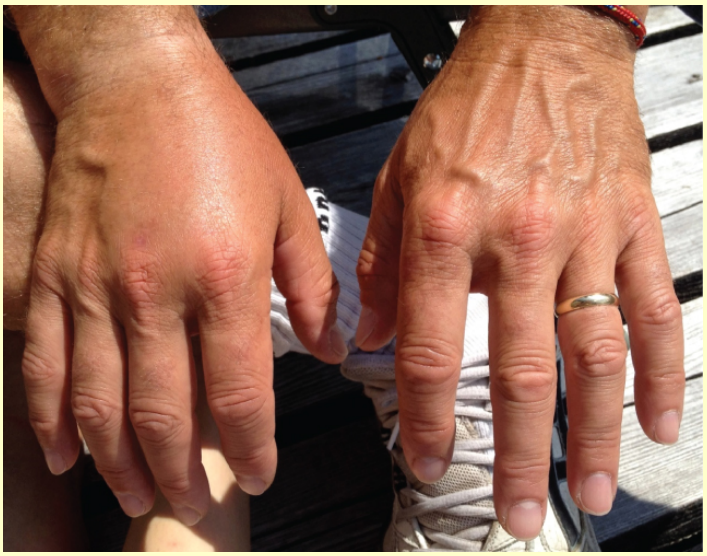


**Figure 26.9 Edema** An allergic reaction can cause capillaries in the hand to leak excess fluid that accumulates in the tissues. (credit: Jane Whitney)

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 though 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.

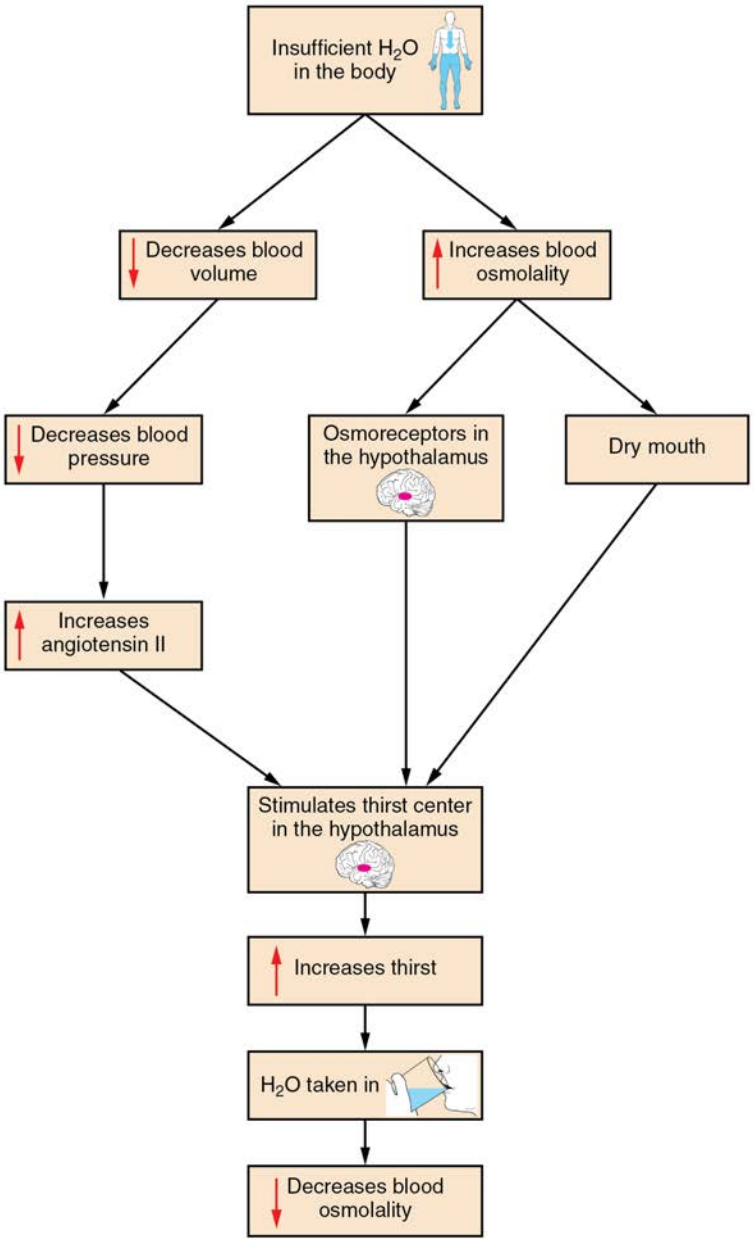



**Figure 26.10 A Flowchart Showing the Thirst Response** The thirst response begins when osmoreceptors detect a decrease in water levels in the blood.

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.

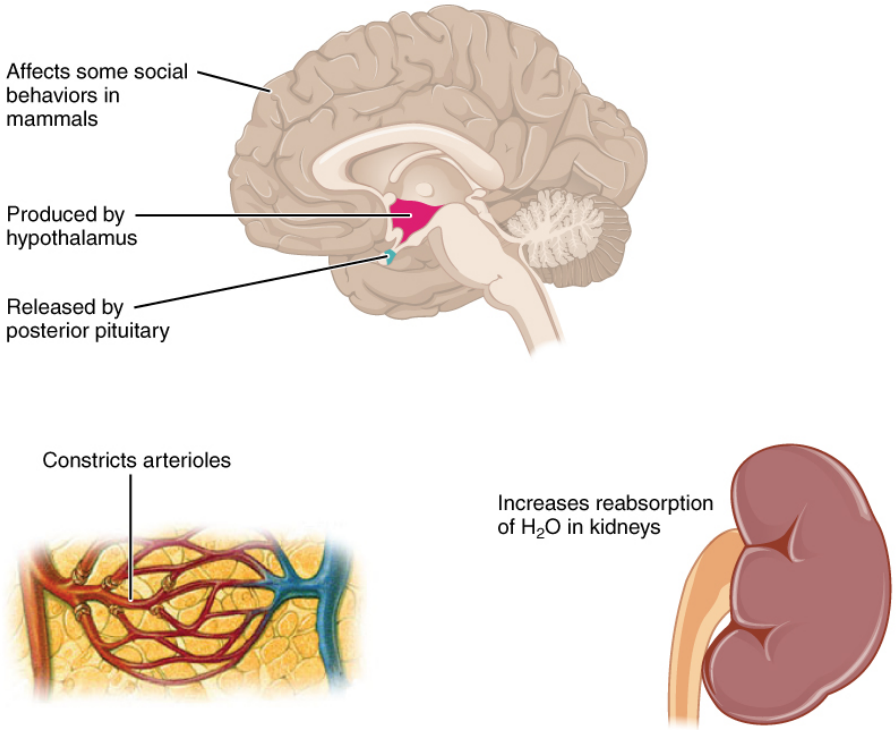



**Figure 26.11 Antidiuretic Hormone (ADH)** ADH is produced in the hypothalamus and released by the posterior pituitary gland. It causes the kidneys to retain water, constricts arterioles in the peripheral circulation, and affects some social behaviors in mammals.

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.

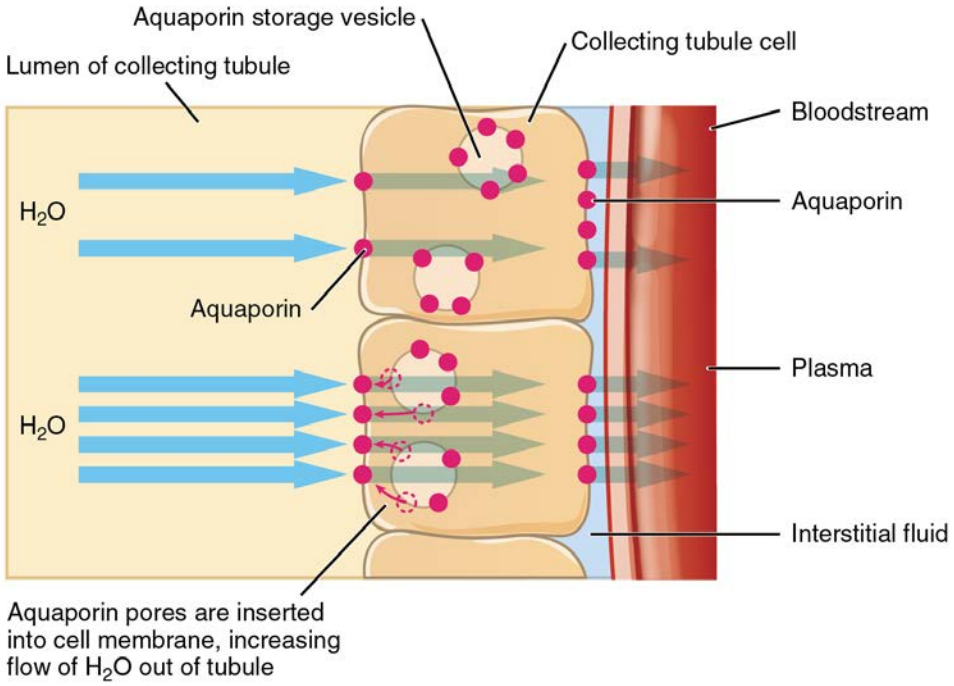



**Figure 26.12 Aquaporins** The binding of ADH to receptors on the cells of the collecting tubule results in aquaporins being inserted into the plasma membrane, shown in the lower cell. This dramatically increases the flow of water out of the tubule and into the bloodstream.

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 | $Na^+$ | 136.00–146.00 (mM) | 138.00–150.00 (mM) | 40.00–220.00 (mM) |
| Potassium | $K^+$ | 3.50–5.00 (mM) | 0.35–3.5 (mM) | 25.00–125.00 (mM) |
| Chloride | $Cl^-$ | 98.00–107.00 (mM) | 118.00–132.00 (mM) | 110.00–250.00 (mM) |
| Bicarbonate | $HCO_3^-$ | 22.00–29.00 (mM) | ------ | ------ |
| Calcium | $Ca^{++}$ | 2.15–2.55 (mmol/day) | ------ | Up to 7.49 (mmol/day) |
| Phosphate | $HPO_4^{2-}$ | 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.

**Hypernatremia** 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.

## Interactive LINK

Watch this **video (http://openstaxcollege.org/l/saltwater)** to see 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 ($CO_2$) and water, two molecules that are produced at the end of aerobic metabolism. Only a small amount of $CO_2$ can be dissolved in body fluids. Thus, over 90 percent of the $CO_2$ is converted into bicarbonate ions, $HCO_3^-$, through the following reactions:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H_2CO_{3-} + H^+$$

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 $CO_2$ 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, $Ca^{2+}$, 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: $H_2PO_{4\ -}$, $HPO_4^{2-}$, and $PO_4^{3-}$. The most common form is $HPO_4^{2-}$. 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**).

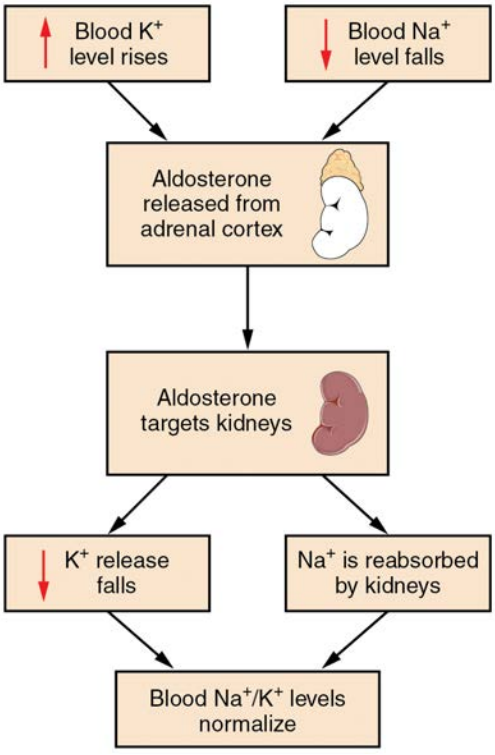



**Figure 26.13 The Aldosterone Feedback Loop** Aldosterone, which is released by the adrenal gland, facilitates reabsorption of $Na^+$ and thus the reabsorption of water.

### 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.

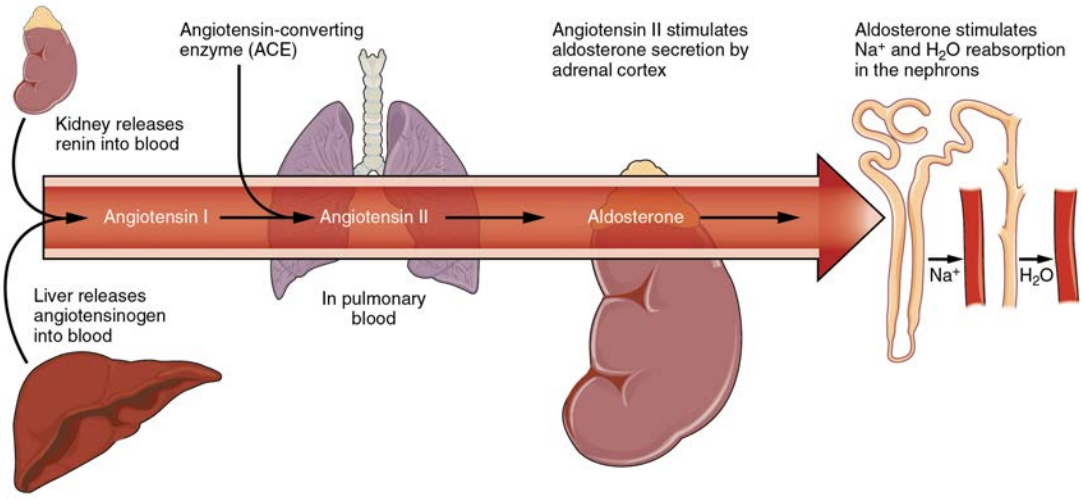



**Figure 26.14 The Renin-Angiotensin System** Angiotensin II stimulates the release of aldosterone from the adrenal cortex.

## 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-balance 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 $CO_2$ from the body. The renal system can also adjust blood pH through the excretion of hydrogen ions ($H^+$) 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 $CO_2$ 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 $CO_2$, 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 ($Na_2H_2PO_4^-$), which is a weak acid, and sodium monohydrogen phosphate ($Na_2HPO_4^{2-}$), which is a weak base. When $Na_2HPO_4^{2-}$ comes into contact with a strong acid, such as HCl, the base picks up a second hydrogen ion to form the weak acid $Na_2H_2PO_4^-$ and sodium chloride, NaCl. When $Na_2HPO_4^{2-}$ (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.

$$HCl + Na_2HPO_4 \rightarrow NaH_2PO_4 + NaCl$$

$$\text{(strong acid)} + \text{(weak base)} \rightarrow \text{(weak acid)} + \text{(salt)}$$

$$NaOH + NaH_2PO_4 \rightarrow Na_2HPO_4 + H_2O$$

$$\text{(strong base)} + \text{(weak acid)} \rightarrow \text{(weak base)} + \text{(water)}$$

### 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 ($NaHCO_3$), comes into contact with a strong acid, such as HCl, carbonic acid ($H_2CO_3$), 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.

$$NaHCO_3 + HCl \rightarrow H_2CO_3 + NaCl$$

$$\text{(sodium bicarbonate)} + \text{(strong acid)} \rightarrow \text{(weak acid)} + \text{(salt)}$$

$$H_2CO_3 + NaOH \rightarrow HCO_{3-} + H_2O$$

$$\text{(weak acid)} + \text{(strong base)} \rightarrow \text{(bicarbonate)} + \text{(water)}$$

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 $CO_2$ 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, $CO_2$ 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**). $CO_2$ in the blood readily reacts with water to form carbonic acid, and the levels of $CO_2$ and carbonic acid in the blood are in equilibrium. When the $CO_2$ level in the blood rises (as it does when you hold your breath), the excess $CO_2$ 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 $CO_2$. The loss of $CO_2$ 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 $CO_2$ 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.

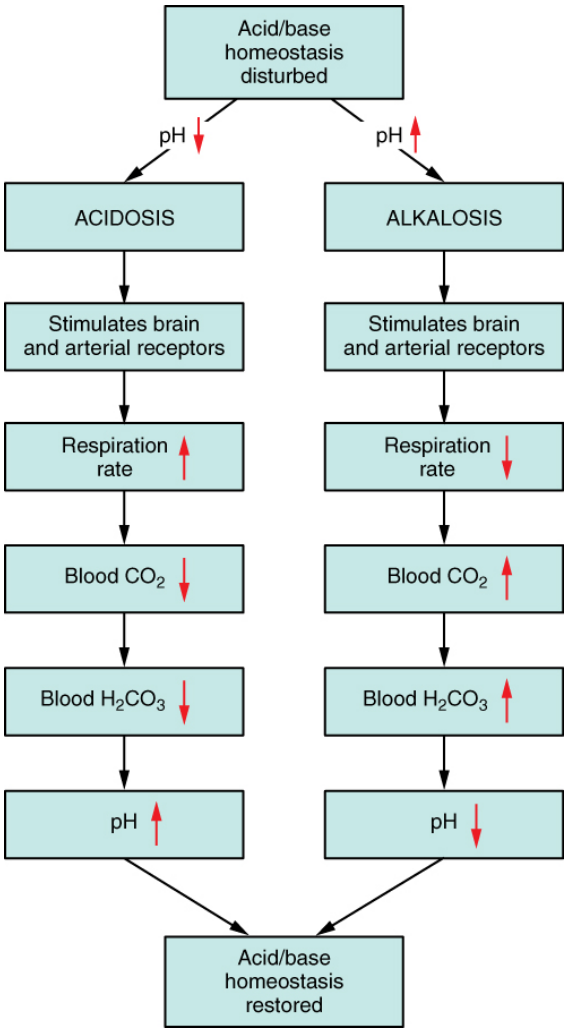



**Figure 26.16 Respiratory Regulation of Blood pH** The respiratory system can reduce blood pH by removing $CO_2$ from the blood.

The chemical reactions that regulate the levels of $CO_2$ 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 $CO_2$ is exhaled. In fact, doubling the respiratory rate for less than 1 minute, removing "extra" $CO_2$, 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 $CO_2$ (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 $CO_2$. This helps to keep you from developing acidosis.

The body regulates the respiratory rate by the use of chemoreceptors, which primarily use $CO_2$ 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 $CO_2$ 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 $CO_2$, 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 $CO_2$, occurs with any cause of hyperventilation that drives off the $CO_2$, 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 $CO_2$, 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, $HCO_3^-$, 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 $H^+$ 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 $CO_2$ 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.

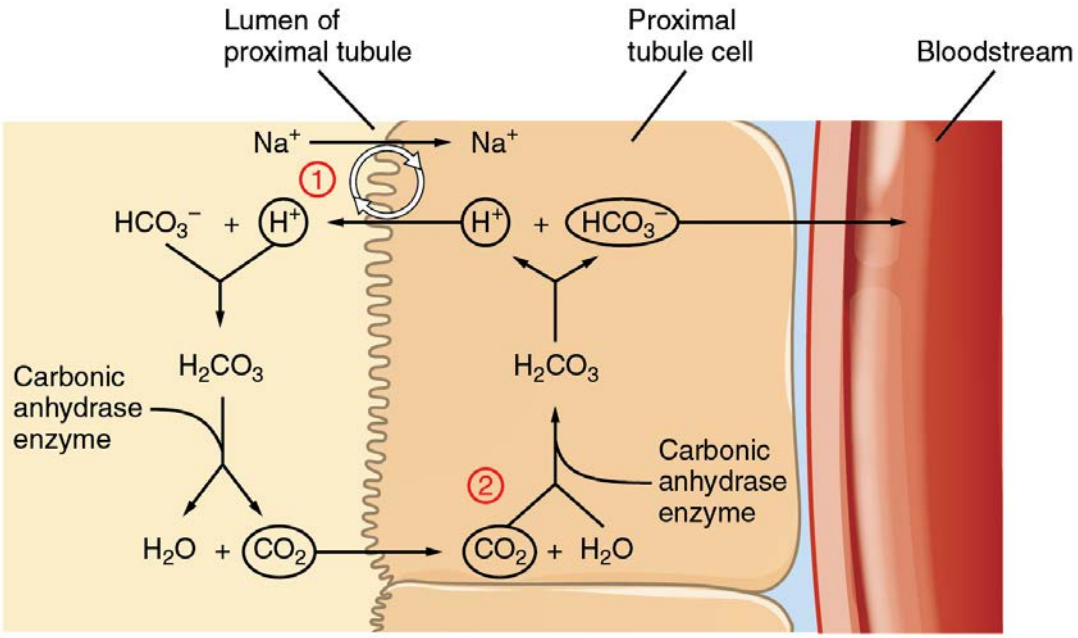



**Figure 26.17 Conservation of Bicarbonate in the Kidney** Tubular cells are not permeable to bicarbonate; thus, bicarbonate is conserved rather than reabsorbed. Steps 1 and 2 of bicarbonate conservation are indicated.

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 $CO_2$. 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 $CO_2$ 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 $CO_2$ 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 $CO_2$ in the body and the amount of $CO_2$ gas exhaled through the lungs. Thus, the respiratory contribution to acid-base balance is usually discussed in terms of $CO_2$ (rather than of carbonic acid). Remember that a molecule of carbonic acid is lost for every molecule of $CO_2$ exhaled, and a molecule of carbonic acid is formed for every molecule of $CO_2$ retained.

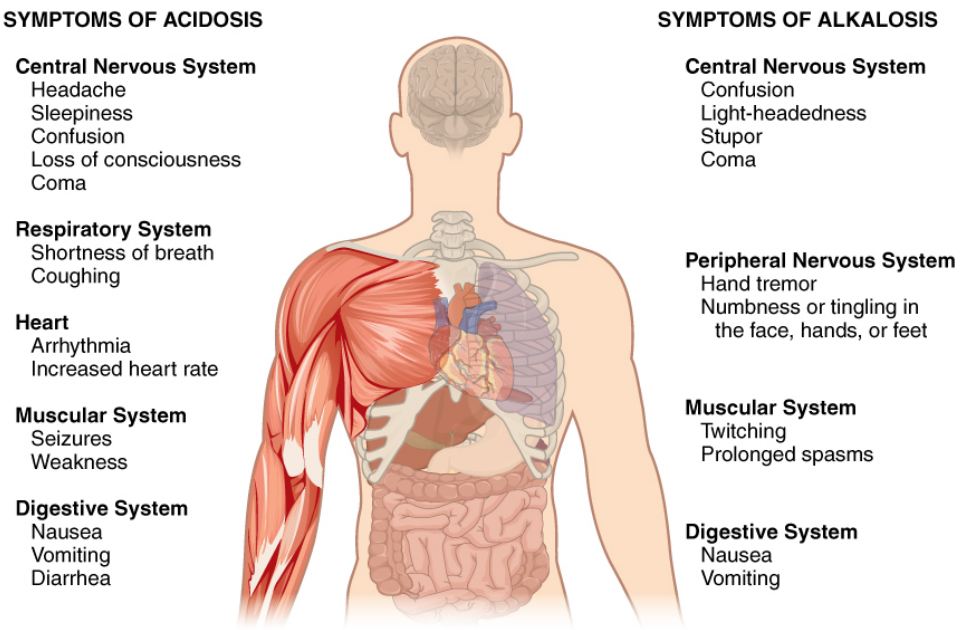



**Figure 26.18 Symptoms of Acidosis and Alkalosis** Symptoms of acidosis affect several organ systems. Both acidosis and alkalosis can be diagnosed using a blood test.

## 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 | β-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/$CO_2$ Excess

**Respiratory acidosis** occurs when the blood is overly acidic due to an excess of carbonic acid, resulting from too much $CO_2$ 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/$CO_2$ Deficiency

**Respiratory alkalosis** occurs when the blood is overly alkaline due to a deficiency in carbonic acid and $CO_2$ levels in the blood. This condition usually occurs when too much $CO_2$ 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)** 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 $CO_2$ 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 $CO_2$ in the blood by decreasing the respiratory rate to conserve $CO_2$. 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 $CO_2$

**hyperchloremia** higher-than-normal blood chloride levels

**hyperkalemia** higher-than-normal blood potassium levels

**hypernatremia** 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 $CO_2$

**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 $CO_2$ causes the blood to be overly acidic

**respiratory alkalosis** condition wherein a deficiency of carbonic acid/$CO_2$ 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, calcitrol, 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 ($OH^-$), or a weak base, which takes up a hydrogen ion ($H^+$). 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 $CO_2$ 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 $CO_2$ 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.** Watch this **video (http://openstaxcollege.org/l/saltwater)** to see 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)** 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 _____.

a. osmotic pressure
b. hydrostatic pressure

c. Brownian movement
d. random motion

**6.** A cation has a(n) _____ charge.
a. neutral
b. positive
c. alternating
d. negative

**7.** Interstitial fluid (IF) is _____.
a. the fluid in the cytosol of the cells
b. the fluid component of blood
c. the fluid that bathes all of the body's cells except for blood cells
d. the intracellular fluids found between membranes

**8.** The largest amount of water comes into the body via _____.
a. metabolism
b. foods
c. liquids
d. humidified air

**9.** The largest amount of water leaves the body via _____.
a. the GI tract
b. the skin as sweat
c. expiration
d. urine

**10.** Insensible water loss is water lost via _____.
a. skin evaporation and in air from the lungs
b. urine
c. excessive sweating
d. vomiting or diarrhea

**11.** How soon after drinking a large glass of water will a person start increasing their urine output?
a. 5 minutes
b. 30 minutes
c. 1 hour
d. 3 hours

**12.** Bone serves as a mineral reserve for which two ions?
a. sodium and potassium
b. calcium and phosphate
c. chloride and bicarbonate
d. calcium and bicarbonate

**13.** Electrolytes are lost mostly through _____.
a. renal function
b. sweating
c. feces
d. respiration

**14.** The major cation in extracellular fluid is _____.
a. sodium
b. potassium
c. chloride
d. bicarbonate

**15.** The major cation in intracellular fluid is _____.
a. sodium
b. potassium
c. chloride
d. bicarbonate

**16.** The major anion in extracellular fluid is _____.
a. sodium
b. potassium
c. chloride
d. bicarbonate

**17.** Most of the body's calcium is found in _____.
a. teeth
b. bone
c. plasma
d. extracellular fluids

**18.** Abnormally increased blood levels of sodium are termed _____.
a. hyperkalemia
b. hyperchloremia
c. hypernatremia
d. hypercalcemia

**19.** The ion with the lowest blood level is _____.
a. sodium
b. potassium
c. chloride
d. bicarbonate

**20.** Which two ions are most affected by aldosterone?
a. sodium and potassium
b. chloride and bicarbonate
c. calcium and phosphate
d. sodium and phosphate

**21.** Which of the following is the most important buffer inside red blood cells?
a. plasma proteins
b. hemoglobin
c. phosphate buffers
d. bicarbonate: carbonic acid buffer

**22.** Which explanation best describes why plasma proteins can function as buffers?
a. Plasma proteins combine with bicarbonate to make a stronger buffer.
b. Plasma proteins are immune to damage from acids.
c. Proteins have both positive and negative charges on their surface.
d. Proteins are alkaline.

**23.** The buffer that is adjusted to control acid-base balance is _____.
a. plasma protein
b. hemoglobin
c. phosphate buffer
d. bicarbonate: carbonic acid buffer

**24.** Carbonic acid levels are controlled through the _____.
a. respiratory system
b. renal system

c. digestive system
d. metabolic rate of cells

**25.** Bicarbonate ion concentrations in the blood are controlled through the _____.

a. respiratory system
b. renal system
c. digestive system
d. metabolic rate of cells

**26.** Which reaction is catalyzed by carbonic anhydrase?

a. $HPO_4^{2-} + H^+ \leftrightarrow H_2PO_{4-}$
b. $CO_2 + H_2O \leftrightarrow H_2CO_3$
c. $H_2PO_{4-} + OH^- \leftrightarrow HPO_4^{2-} + H_2O$
d. $H_2CO_3 \leftrightarrow HCO_{3-} + H^+$

**27.** Which of the following is a cause of metabolic acidosis?

a. excessive HCl loss
b. increased aldosterone
c. diarrhea
d. prolonged use of diuretics

**28.** Which of the following is a cause of respiratory acidosis?

a. emphysema
b. low blood $K^+$
c. increased aldosterone
d. increased blood ketones

**29.** At a pH of 7.40, the carbonic acid ratio is _____.

a. 35:1
b. 4:1
c. 20:1
d. 3:1

**30.** Which of the following is characterized as metabolic alkalosis?

a. increased pH, decreased $pCO_2$, decreased $HCO_3^-$
b. increased pH, increased $pCO_2$, increased $HCO_3^-$
c. decreased pH, decreased $pCO_2$, decreased $HCO_3^-$
d. decreased pH, increased $pCO_2$, increased $HCO_3^-$

## 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 $CO_2$ 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, $pCO_2$ higher than normal, and total $HCO_3^-$ 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, $pCO_2$ in the normal range, and total $HCO_3^-$ 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.

# 27 | THE REPRODUCTIVE SYSTEM

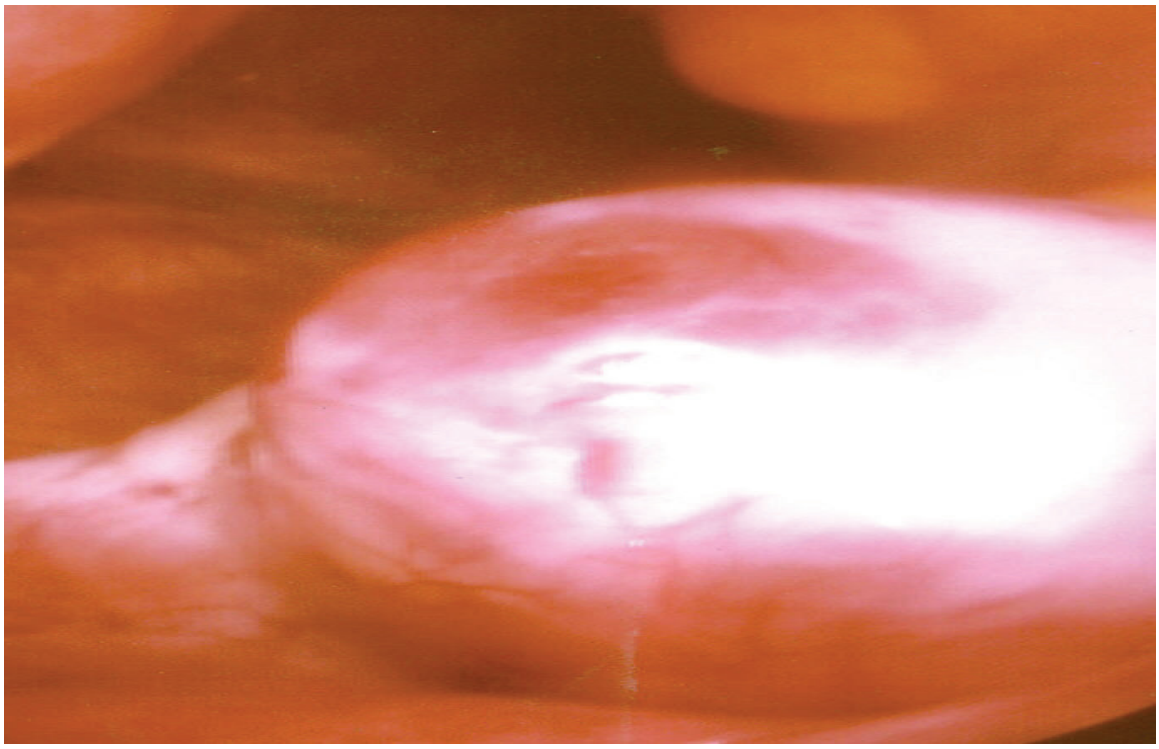


**Figure 27.1 Ovulation** Following a surge of luteinizing hormone (LH), an oocyte (immature egg cell) will be released into the uterine tube, where it will then be available to be fertilized by a male's sperm. Ovulation marks the end of the follicular phase of the ovarian cycle and the start of the luteal phase.

## Introduction

### Chapter Objectives

After studying this chapter, you will be able to:

- Describe the anatomy of the male and female reproductive systems, including their accessory structures
- Explain the role of hypothalamic and pituitary hormones in male and female reproductive function
- Trace the path of a sperm cell from its initial production through fertilization of an oocyte
- Explain the events in the ovary prior to ovulation
- Describe the development and maturation of the sex organs and the emergence of secondary sex characteristics during puberty

Small, uncoordinated, and slick with amniotic fluid, a newborn encounters the world outside of her mother's womb. We do not often consider that a child's birth is proof of the healthy functioning of both her mother's and father's reproductive systems. Moreover, her parents' endocrine systems had to secrete the appropriate regulating hormones to induce the production and release of unique male and female gametes, reproductive cells containing the parents' genetic material (one set of 23 chromosomes). Her parent's reproductive behavior had to facilitate the transfer of male gametes—the sperm—to the female reproductive tract at just the right time to encounter the female gamete, an oocyte (egg). Finally, combination

of the gametes (fertilization) had to occur, followed by implantation and development. In this chapter, you will explore the male and female reproductive systems, whose healthy functioning can culminate in the powerful sound of a newborn's first cry.

# 27.1 | Anatomy and Physiology of the Male Reproductive System

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

- Describe the structure and function of the organs of the male reproductive system
- Describe the structure and function of the sperm cell
- Explain the events during spermatogenesis that produce haploid sperm from diploid cells
- Identify the importance of testosterone in male reproductive function

Unique for its role in human reproduction, a **gamete** is a specialized sex cell carrying 23 chromosomes—one half the number in body cells. At fertilization, the chromosomes in one male gamete, called a **sperm** (or spermatozoon), combine with the chromosomes in one female gamete, called an oocyte. The function of the male reproductive system (**Figure 27.2**) is to produce sperm and transfer them to the female reproductive tract. The paired testes are a crucial component in this process, as they produce both sperm and androgens, the hormones that support male reproductive physiology. In humans, the most important male androgen is testosterone. Several accessory organs and ducts aid the process of sperm maturation and transport the sperm and other seminal components to the penis, which delivers sperm to the female reproductive tract. In this section, we examine each of these different structures, and discuss the process of sperm production and transport.

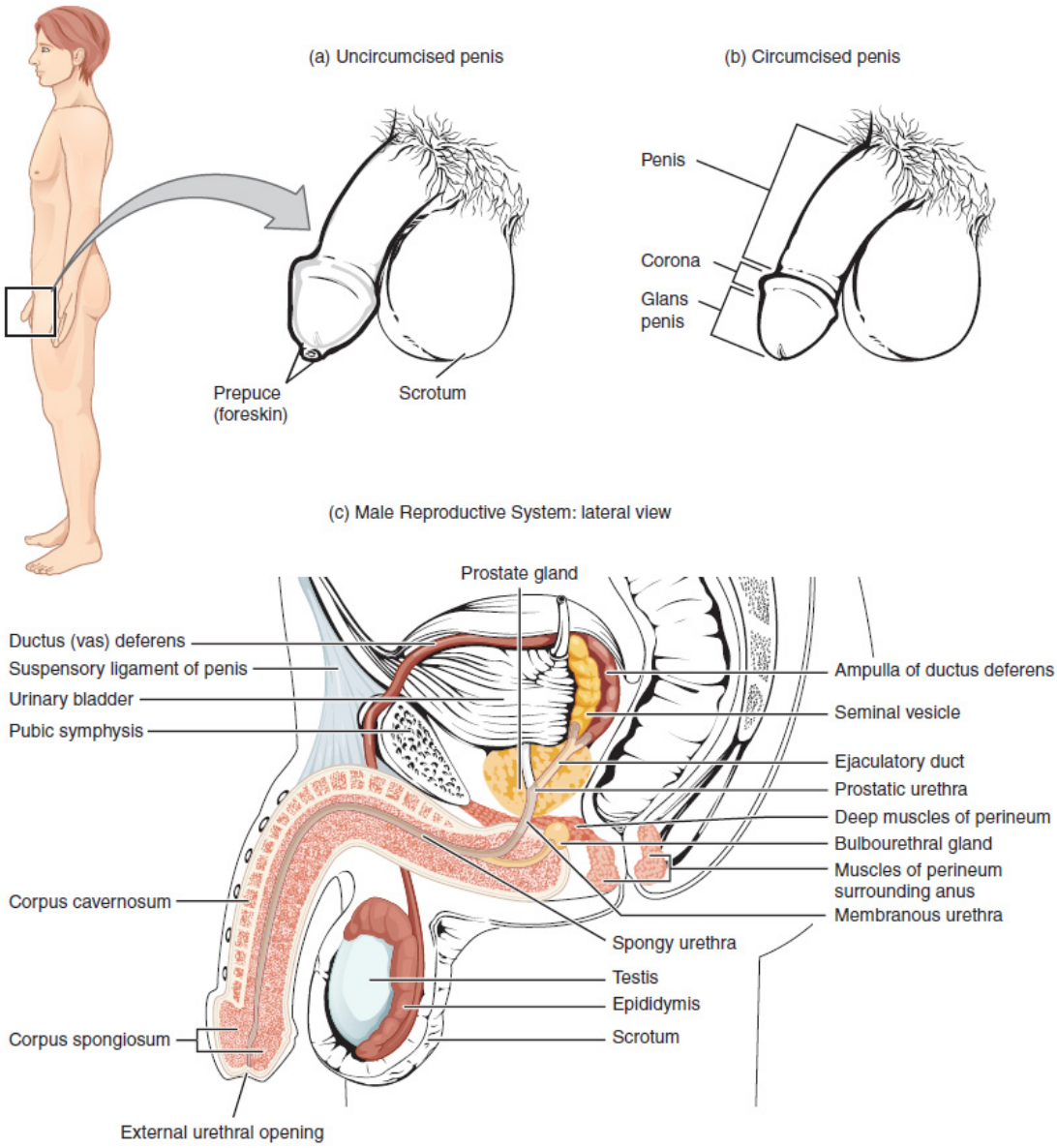



**Figure 27.2 Male Reproductive System** The structures of the male reproductive system include the testes, the epididymides, the penis, and the ducts and glands that produce and carry semen. Sperm exit the scrotum through the ductus deferens, which is bundled in the spermatic cord. The seminal vesicles and prostate gland add fluids to the sperm to create semen.

## Scrotum

The testes are located in a skin-covered, highly pigmented, muscular sack called the **scrotum** that extends from the body behind the penis (see **Figure 27.2**). This location is important in sperm production, which occurs within the testes, and proceeds more efficiently when the testes are kept 2 to 4°C below core body temperature.

The dartos muscle makes up the subcutaneous muscle layer of the scrotum (**Figure 27.3**). It continues internally to make up the scrotal septum, a wall that divides the scrotum into two compartments, each housing one testis. Descending from the internal oblique muscle of the abdominal wall are the two cremaster muscles, which cover each testis like a muscular net. By contracting simultaneously, the dartos and cremaster muscles can elevate the testes in cold weather (or water), moving the testes closer to the body and decreasing the surface area of the scrotum to retain heat. Alternatively, as the environmental temperature increases, the scrotum relaxes, moving the testes farther from the body core and increasing scrotal surface area, which promotes heat loss. Externally, the scrotum has a raised medial thickening on the surface called the raphae.

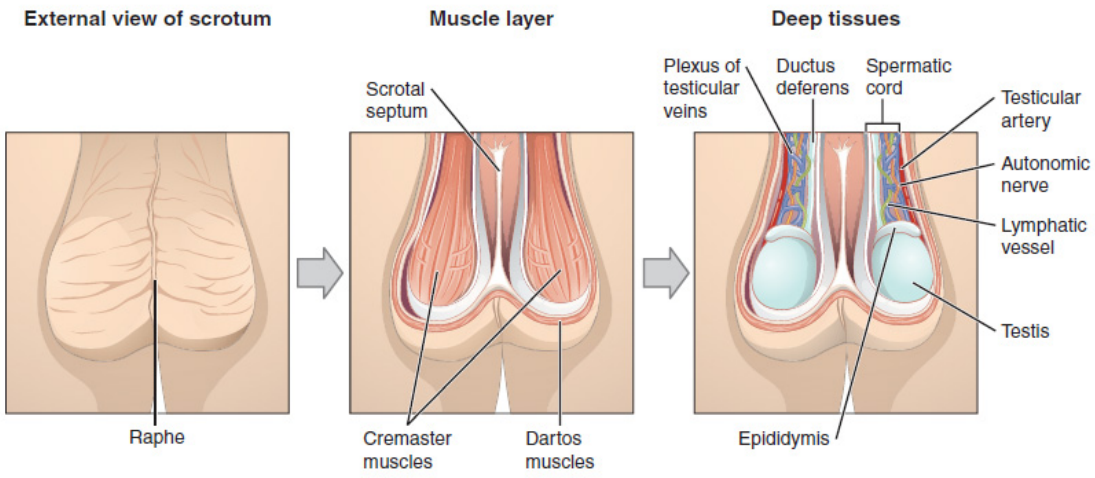



**Figure 27.3 The Scrotum and Testes** This anterior view shows the structures of the scrotum and testes.

## Testes

The **testes** (singular = testis) are the male **gonads**—that is, the male reproductive organs. They produce both sperm and androgens, such as testosterone, and are active throughout the reproductive lifespan of the male.

Paired ovals, the testes are each approximately 4 to 5 cm in length and are housed within the scrotum (see **Figure 27.3**). They are surrounded by two distinct layers of protective connective tissue (**Figure 27.4**). The outer tunica vaginalis is a serous membrane that has both a parietal and a thin visceral layer. Beneath the tunica vaginalis is the tunica albuginea, a tough, white, dense connective tissue layer covering the testis itself. Not only does the tunica albuginea cover the outside of the testis, it also invaginates to form septa that divide the testis into 300 to 400 structures called lobules. Within the lobules, sperm develop in structures called seminiferous tubules. During the seventh month of the developmental period of a male fetus, each testis moves through the abdominal musculature to descend into the scrotal cavity. This is called the “descent of the testis.” Cryptorchidism is the clinical term used when one or both of the testes fail to descend into the scrotum prior to birth.

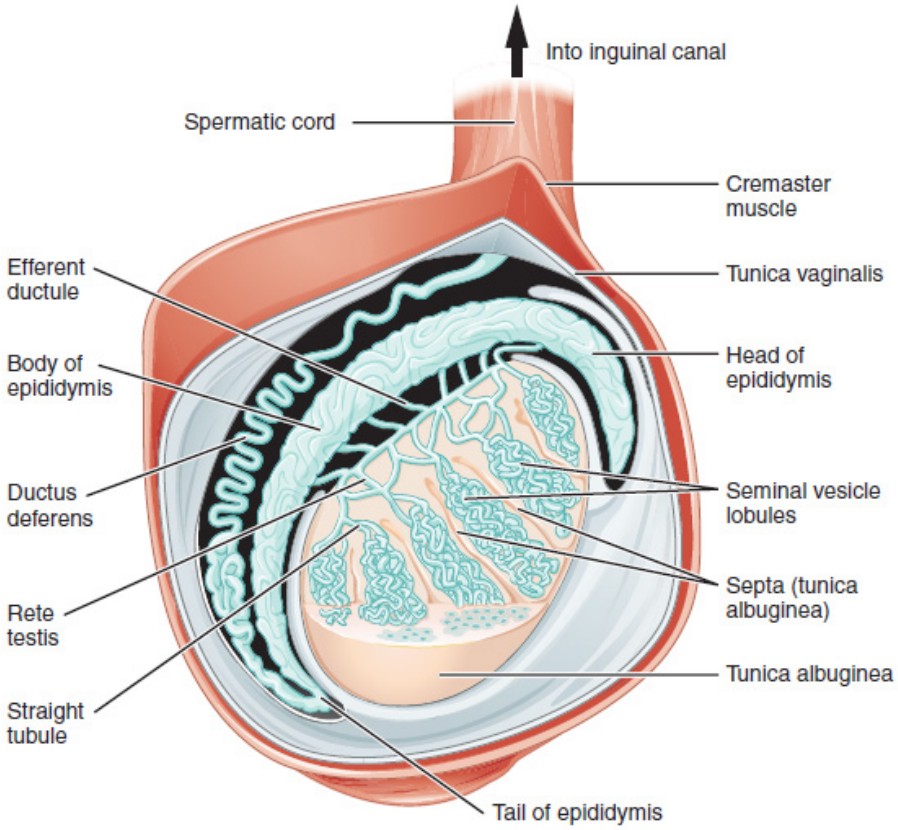



**Figure 27.4 Anatomy of the Testis** This sagittal view shows the seminiferous tubules, the site of sperm production. Formed sperm are transferred to the epididymis, where they mature. They leave the epididymis during an ejaculation via the ductus deferens.

The tightly coiled **seminiferous tubules** form the bulk of each testis. They are composed of developing sperm cells surrounding a lumen, the hollow center of the tubule, where formed sperm are released into the duct system of the testis. Specifically, from the lumens of the seminiferous tubules, sperm move into the straight tubules (or tubuli recti), and from there into a fine meshwork of tubules called the rete testes. Sperm leave the rete testes, and the testis itself, through the 15 to 20 efferent ductules that cross the tunica albuginea.

Inside the seminiferous tubules are six different cell types. These include supporting cells called sustentacular cells, as well as five types of developing sperm cells called germ cells. Germ cell development progresses from the basement membrane—at the perimeter of the tubule—toward the lumen. Let's look more closely at these cell types.

### Sertoli Cells

Surrounding all stages of the developing sperm cells are elongate, branching **Sertoli cells**. Sertoli cells are a type of supporting cell called a sustentacular cell, or sustenocyte, that are typically found in epithelial tissue. Sertoli cells secrete signaling molecules that promote sperm production and can control whether germ cells live or die. They extend physically around the germ cells from the peripheral basement membrane of the seminiferous tubules to the lumen. Tight junctions between these sustentacular cells create the **blood–testis barrier**, which keeps bloodborne substances from reaching the germ cells and, at the same time, keeps surface antigens on developing germ cells from escaping into the bloodstream and prompting an autoimmune response.

### Germ Cells

The least mature cells, the **spermatogonia** (singular = spermatogonium), line the basement membrane inside the tubule. Spermatogonia are the stem cells of the testis, which means that they are still able to differentiate into a variety of different cell types throughout adulthood. Spermatogonia divide to produce primary and secondary spermatocytes, then spermatids, which finally produce formed sperm. The process that begins with spermatogonia and concludes with the production of sperm is called **spermatogenesis**.

### Spermatogenesis

As just noted, spermatogenesis occurs in the seminiferous tubules that form the bulk of each testis (see **Figure 27.4**). The process begins at puberty, after which time sperm are produced constantly throughout a man's life. One production cycle, from spermatogonia through formed sperm, takes approximately 64 days. A new cycle starts approximately every 16 days,

although this timing is not synchronous across the seminiferous tubules. Sperm counts—the total number of sperm a man produces—slowly decline after age 35, and some studies suggest that smoking can lower sperm counts irrespective of age.

The process of spermatogenesis begins with mitosis of the diploid spermatogonia (Figure 27.5). Because these cells are diploid (2*n*), they each have a complete copy of the father's genetic material, or 46 chromosomes. However, mature gametes are haploid (1*n*), containing 23 chromosomes—meaning that daughter cells of spermatogonia must undergo a second cellular division through the process of meiosis.

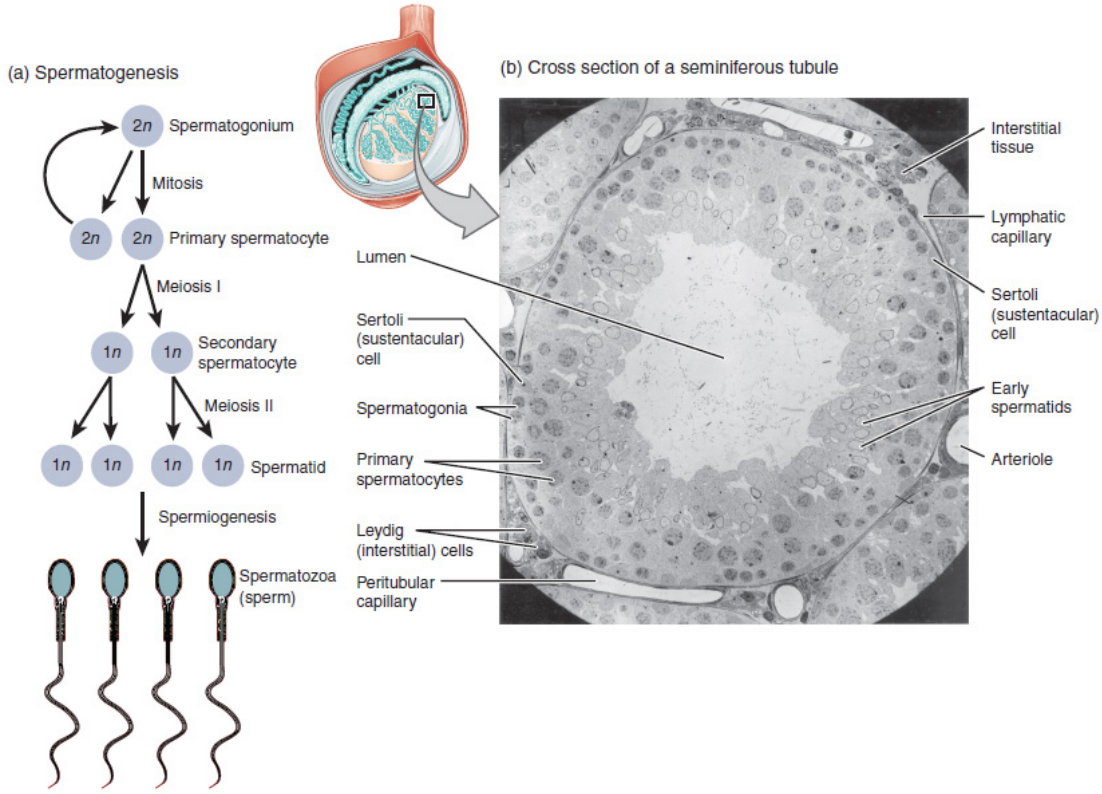



**Figure 27.5 Spermatogenesis** (a) Mitosis of a spermatogonial stem cell involves a single cell division that results in two identical, diploid daughter cells (spermatogonia to primary spermatocyte). Meiosis has two rounds of cell division: primary spermatocyte to secondary spermatocyte, and then secondary spermatocyte to spermatid. This produces four haploid daughter cells (spermatids). (b) In this electron micrograph of a cross-section of a seminiferous tubule from a rat, the lumen is the light-shaded area in the center of the image. The location of the primary spermatocytes is near the basement membrane, and the early spermatids are approaching the lumen (tissue source: rat). EM × 900. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Two identical diploid cells result from spermatogonia mitosis. One of these cells remains a spermatogonium, and the other becomes a primary **spermatocyte**, the next stage in the process of spermatogenesis. As in mitosis, DNA is replicated in a primary spermatocyte, and the cell undergoes cell division to produce two cells with identical chromosomes. Each of these is a secondary spermatocyte. Now a second round of cell division occurs in both of the secondary spermatocytes, separating the chromosome pairs. This second meiotic division results in a total of four cells with only half of the number of chromosomes. Each of these new cells is a **spermatid**. Although haploid, early spermatids look very similar to cells in the earlier stages of spermatogenesis, with a round shape, central nucleus, and large amount of cytoplasm. A process called **spermiogenesis** transforms these early spermatids, reducing the cytoplasm, and beginning the formation of the parts of a true sperm. The fifth stage of germ cell formation—spermatozoa, or formed sperm—is the end result of this process, which occurs in the portion of the tubule nearest the lumen. Eventually, the sperm are released into the lumen and are moved along a series of ducts in the testis toward a structure called the epididymis for the next step of sperm maturation.

## Structure of Formed Sperm

Sperm are smaller than most cells in the body; in fact, the volume of a sperm cell is 85,000 times less than that of the female gamete. Approximately 100 to 300 million sperm are produced each day, whereas women typically ovulate only one oocyte per month as is true for most cells in the body, the structure of sperm cells speaks to their function. Sperm have a distinctive head, mid-piece, and tail region (Figure 27.6). The head of the sperm contains the extremely compact haploid nucleus with very little cytoplasm. These qualities contribute to the overall small size of the sperm (the head is only 5 $\mu$m long). A structure called the acrosome covers most of the head of the sperm cell as a "cap" that is filled with lysosomal enzymes important for preparing sperm to participate in fertilization. Tightly packed mitochondria fill the mid-piece of the sperm. ATP produced by these mitochondria will power the flagellum, which extends from the neck and the mid-piece through the

tail of the sperm, enabling it to move the entire sperm cell. The central strand of the flagellum, the axial filament, is formed from one centriole inside the maturing sperm cell during the final stages of spermatogenesis.

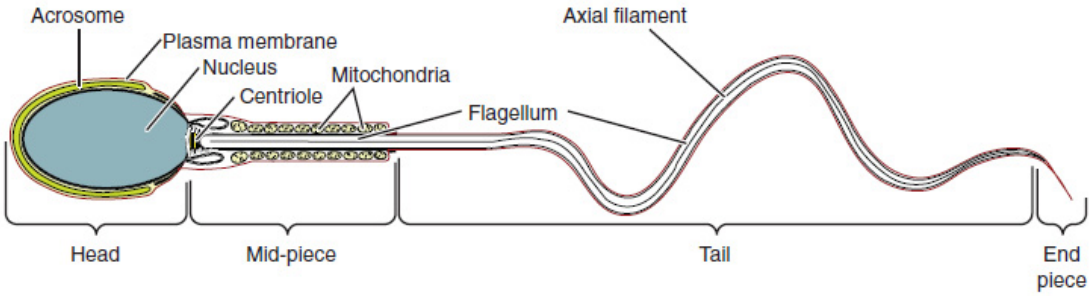



**Figure 27.6 Structure of Sperm** Sperm cells are divided into a head, containing DNA; a mid-piece, containing mitochondria; and a tail, providing motility. The acrosome is oval and somewhat flattened.

## Sperm Transport

To fertilize an egg, sperm must be moved from the seminiferous tubules in the testes, through the epididymis, and—later during ejaculation—along the length of the penis and out into the female reproductive tract.

### Role of the Epididymis

From the lumen of the seminiferous tubules, the immotile sperm are surrounded by testicular fluid and moved to the **epididymis** (plural = epididymides), a coiled tube attached to the testis where newly formed sperm continue to mature (see Figure 27.4). Though the epididymis does not take up much room in its tightly coiled state, it would be approximately 6 m (20 feet) long if straightened. It takes an average of 12 days for sperm to move through the coils of the epididymis, with the shortest recorded transit time in humans being one day. Sperm enter the head of the epididymis and are moved along predominantly by the contraction of smooth muscles lining the epididymal tubes. As they are moved along the length of the epididymis, the sperm further mature and acquire the ability to move under their own power. Once inside the female reproductive tract, they will use this ability to move independently toward the unfertilized egg. The more mature sperm are then stored in the tail of the epididymis (the final section) until ejaculation occurs.

### Duct System

During ejaculation, sperm exit the tail of the epididymis and are pushed by smooth muscle contraction to the **ductus deferens** (also called the vas deferens). The ductus deferens is a thick, muscular tube that is bundled together inside the scrotum with connective tissue, blood vessels, and nerves into a structure called the **spermatic cord** (see Figure 27.2 and Figure 27.3). Because the ductus deferens is physically accessible within the scrotum, surgical sterilization to interrupt sperm delivery can be performed by cutting and sealing a small section of the ductus (vas) deferens. This procedure is called a vasectomy, and it is an effective form of male birth control. Although it may be possible to reverse a vasectomy, clinicians consider the procedure permanent, and advise men to undergo it only if they are certain they no longer wish to father children.

**Interactive LINK**

Watch this **video (http://openstaxcollege.org/l/vasectomy)** to learn about a vasectomy. As described in this video, a vasectomy is a procedure in which a small section of the ductus (vas) deferens is removed from the scrotum. This interrupts the path taken by sperm through the ductus deferens. If sperm do not exit through the vas, either because the man has had a vasectomy or has not ejaculated, in what region of the testis do they remain?

From each epididymis, each ductus deferens extends superiorly into the abdominal cavity through the **inguinal canal** in the abdominal wall. From here, the ductus deferens continues posteriorly to the pelvic cavity, ending posterior to the bladder where it dilates in a region called the ampulla (meaning “flask”).

Sperm make up only 5 percent of the final volume of **semen**, the thick, milky fluid that the male ejaculates. The bulk of semen is produced by three critical accessory glands of the male reproductive system: the seminal vesicles, the prostate, and the bulbourethral glands.

## Seminal Vesicles

As sperm pass through the ampulla of the ductus deferens at ejaculation, they mix with fluid from the associated **seminal vesicle** (see **Figure 27.2**). The paired seminal vesicles are glands that contribute approximately 60 percent of the semen volume. Seminal vesicle fluid contains large amounts of fructose, which is used by the sperm mitochondria to generate ATP to allow movement through the female reproductive tract.

The fluid, now containing both sperm and seminal vesicle secretions, next moves into the associated **ejaculatory duct**, a short structure formed from the ampulla of the ductus deferens and the duct of the seminal vesicle. The paired ejaculatory ducts transport the seminal fluid into the next structure, the prostate gland.

## Prostate Gland

As shown in **Figure 27.2**, the centrally located **prostate gland** sits anterior to the rectum at the base of the bladder surrounding the prostatic urethra (the portion of the urethra that runs within the prostate). About the size of a walnut, the prostate is formed of both muscular and glandular tissues. It excretes an alkaline, milky fluid to the passing seminal fluid—now called semen—that is critical to first coagulate and then decoagulate the semen following ejaculation. The temporary thickening of semen helps retain it within the female reproductive tract, providing time for sperm to utilize the fructose provided by seminal vesicle secretions. When the semen regains its fluid state, sperm can then pass farther into the female reproductive tract.

The prostate normally doubles in size during puberty. At approximately age 25, it gradually begins to enlarge again. This enlargement does not usually cause problems; however, abnormal growth of the prostate, or benign prostatic hyperplasia (BPH), can cause constriction of the urethra as it passes through the middle of the prostate gland, leading to a number of lower urinary tract symptoms, such as a frequent and intense urge to urinate, a weak stream, and a sensation that the bladder has not emptied completely. By age 60, approximately 40 percent of men have some degree of BPH. By age 80, the number of affected individuals has jumped to as many as 80 percent. Treatments for BPH attempt to relieve the pressure on the urethra so that urine can flow more normally. Mild to moderate symptoms are treated with medication, whereas severe enlargement of the prostate is treated by surgery in which a portion of the prostate tissue is removed.

Another common disorder involving the prostate is prostate cancer. According to the Centers for Disease Control and Prevention (CDC), prostate cancer is the second most common cancer in men. However, some forms of prostate cancer grow very slowly and thus may not ever require treatment. Aggressive forms of prostate cancer, in contrast, involve metastasis to vulnerable organs like the lungs and brain. There is no link between BPH and prostate cancer, but the symptoms are similar. Prostate cancer is detected by a medical history, a blood test, and a rectal exam that allows physicians to palpate the prostate and check for unusual masses. If a mass is detected, the cancer diagnosis is confirmed by biopsy of the cells.

## Bulbourethral Glands

The final addition to semen is made by two **bulbourethral glands** (or Cowper’s glands) that release a thick, salty fluid that lubricates the end of the urethra and the vagina, and helps to clean urine residues from the penile urethra. The fluid from these accessory glands is released after the male becomes sexually aroused, and shortly before the release of the semen. It is therefore sometimes called pre-ejaculate. It is important to note that, in addition to the lubricating proteins, it is possible for bulbourethral fluid to pick up sperm already present in the urethra, and therefore it may be able to cause pregnancy.

**Interactive LINK**

Watch this **video (http://openstaxcollege.org/l/spermpath)** to explore the structures of the male reproductive system and the path of sperm, which starts in the testes and ends as the sperm leave the penis through the urethra. Where are sperm deposited after they leave the ejaculatory duct?

## The Penis

The **penis** is the male organ of copulation (sexual intercourse). It is flaccid for non-sexual actions, such as urination, and turgid and rod-like with sexual arousal. When erect, the stiffness of the organ allows it to penetrate into the vagina and deposit semen into the female reproductive tract.

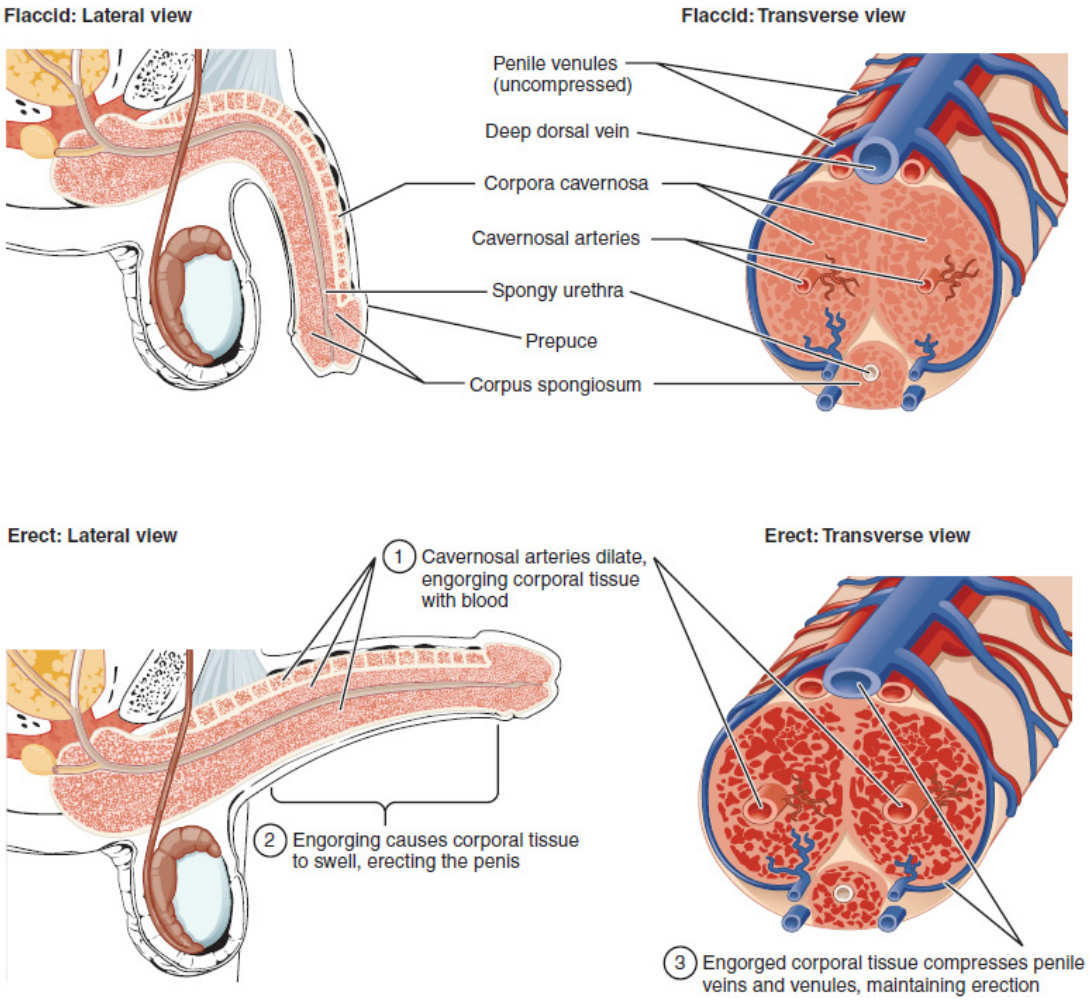



**Figure 27.7 Cross-Sectional Anatomy of the Penis** Three columns of erectile tissue make up most of the volume of the penis.

The shaft of the penis surrounds the urethra (Figure 27.7). The shaft is composed of three column-like chambers of erectile tissue that span the length of the shaft. Each of the two larger lateral chambers is called a **corpus cavernosum**

(plural = corpora cavernosa). Together, these make up the bulk of the penis. The **corpus spongiosum**, which can be felt as a raised ridge on the erect penis, is a smaller chamber that surrounds the spongy, or penile, urethra. The end of the penis, called the **glans penis**, has a high concentration of nerve endings, resulting in very sensitive skin that influences the likelihood of ejaculation (see **Figure 27.2**). The skin from the shaft extends down over the glans and forms a collar called the **prepuce** (or foreskin). The foreskin also contains a dense concentration of nerve endings, and both lubricate and protect the sensitive skin of the glans penis. A surgical procedure called circumcision, often performed for religious or social reasons, removes the prepuce, typically within days of birth.

Both sexual arousal and REM sleep (during which dreaming occurs) can induce an erection. Penile erections are the result of vasocongestion, or engorgement of the tissues because of more arterial blood flowing into the penis than is leaving in the veins. During sexual arousal, nitric oxide (NO) is released from nerve endings near blood vessels within the corpora cavernosa and spongiosum. Release of NO activates a signaling pathway that results in relaxation of the smooth muscles that surround the penile arteries, causing them to dilate. This dilation increases the amount of blood that can enter the penis and induces the endothelial cells in the penile arterial walls to also secrete NO and perpetuate the vasodilation. The rapid increase in blood volume fills the erectile chambers, and the increased pressure of the filled chambers compresses the thin-walled penile venules, preventing venous drainage of the penis. The result of this increased blood flow to the penis and reduced blood return from the penis is erection. Depending on the flaccid dimensions of a penis, it can increase in size slightly or greatly during erection, with the average length of an erect penis measuring approximately 15 cm.

## Disorders of the...

### Male Reproductive System

Erectile dysfunction (ED) is a condition in which a man has difficulty either initiating or maintaining an erection. The combined prevalence of minimal, moderate, and complete ED is approximately 40 percent in men at age 40, and reaches nearly 70 percent by 70 years of age. In addition to aging, ED is associated with diabetes, vascular disease, psychiatric disorders, prostate disorders, the use of some drugs such as certain antidepressants, and problems with the testes resulting in low testosterone concentrations. These physical and emotional conditions can lead to interruptions in the vasodilation pathway and result in an inability to achieve an erection.

Recall that the release of NO induces relaxation of the smooth muscles that surround the penile arteries, leading to the vasodilation necessary to achieve an erection. To reverse the process of vasodilation, an enzyme called phosphodiesterase (PDE) degrades a key component of the NO signaling pathway called cGMP. There are several different forms of this enzyme, and PDE type 5 is the type of PDE found in the tissues of the penis. Scientists discovered that inhibiting PDE5 increases blood flow, and allows vasodilation of the penis to occur.

PDEs and the vasodilation signaling pathway are found in the vasculature in other parts of the body. In the 1990s, clinical trials of a PDE5 inhibitor called sildenafil were initiated to treat hypertension and angina pectoris (chest pain caused by poor blood flow through the heart). The trial showed that the drug was not effective at treating heart conditions, but many men experienced erection and priapism (erection lasting longer than 4 hours). Because of this, a clinical trial was started to investigate the ability of sildenafil to promote erections in men suffering from ED. In 1998, the FDA approved the drug, marketed as Viagra®. Since approval of the drug, sildenafil and similar PDE inhibitors now generate over a billion dollars a year in sales, and are reported to be effective in treating approximately 70 to 85 percent of cases of ED. Importantly, men with health problems—especially those with cardiac disease taking nitrates—should avoid Viagra or talk to their physician to find out if they are a candidate for the use of this drug, as deaths have been reported for at-risk users.

## Testosterone

Testosterone, an androgen, is a steroid hormone produced by **Leydig cells**. The alternate term for Leydig cells, interstitial cells, reflects their location between the seminiferous tubules in the testes. In male embryos, testosterone is secreted by Leydig cells by the seventh week of development, with peak concentrations reached in the second trimester. This early release of testosterone results in the anatomical differentiation of the male sexual organs. In childhood, testosterone concentrations are low. They increase during puberty, activating characteristic physical changes and initiating spermatogenesis.

### Functions of Testosterone

The continued presence of testosterone is necessary to keep the male reproductive system working properly, and Leydig cells produce approximately 6 to 7 mg of testosterone per day. Testicular steroidogenesis (the manufacture of androgens, including testosterone) results in testosterone concentrations that are 100 times higher in the testes than in the circulation. Maintaining these normal concentrations of testosterone promotes spermatogenesis, whereas low levels of testosterone can lead to infertility. In addition to intratesticular secretion, testosterone is also released into the systemic circulation and plays an important role in muscle development, bone growth, the development of secondary sex characteristics, and maintaining

libido (sex drive) in both males and females. In females, the ovaries secrete small amounts of testosterone, although most is converted to estradiol. A small amount of testosterone is also secreted by the adrenal glands in both sexes.

## Control of Testosterone

The regulation of testosterone concentrations throughout the body is critical for male reproductive function. The intricate interplay between the endocrine system and the reproductive system is shown in **Figure 27.8**.

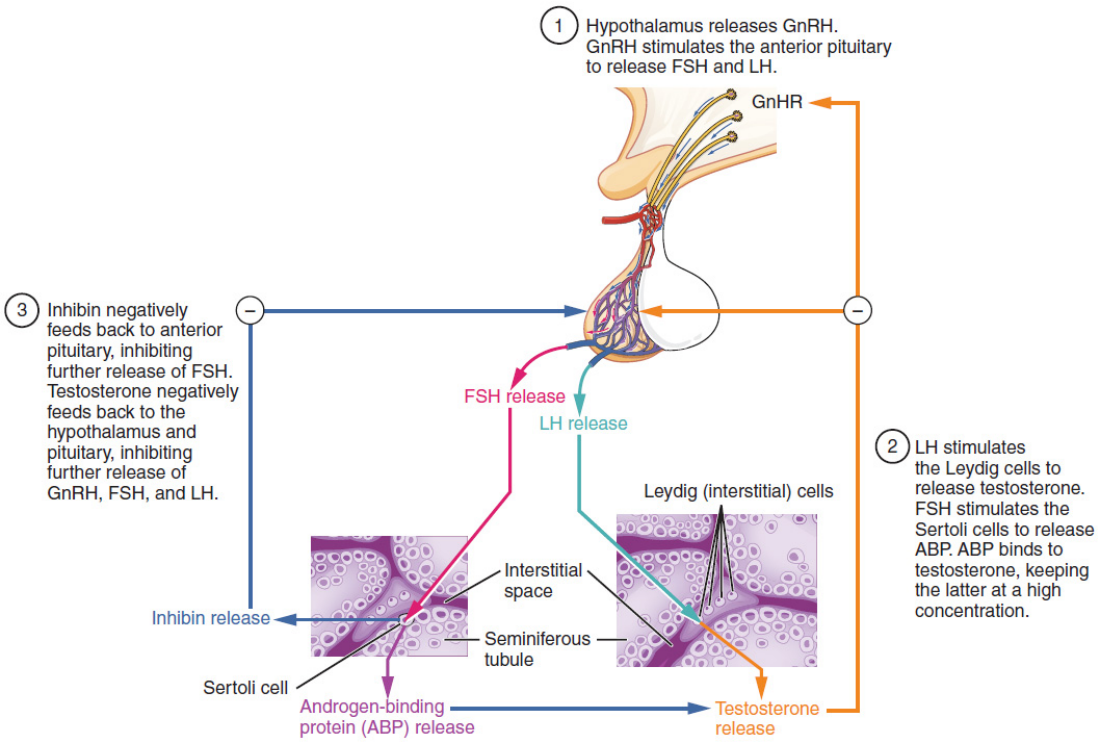



**Figure 27.8 Regulation of Testosterone Production** The hypothalamus and pituitary gland regulate the production of testosterone and the cells that assist in spermatogenesis. GnRH activates the anterior pituitary to produce LH and FSH, which in turn stimulate Leydig cells and Sertoli cells, respectively. The system is a negative feedback loop because the end products of the pathway, testosterone and inhibin, interact with the activity of GnRH to inhibit their own production.

The regulation of Leydig cell production of testosterone begins outside of the testes. The hypothalamus and the pituitary gland in the brain integrate external and internal signals to control testosterone synthesis and secretion. The regulation begins in the hypothalamus. Pulsatile release of a hormone called **gonadotropin-releasing hormone (GnRH)** from the hypothalamus stimulates the endocrine release of hormones from the pituitary gland. Binding of GnRH to its receptors on the anterior pituitary gland stimulates release of the two gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These two hormones are critical for reproductive function in both men and women. In men, FSH binds predominantly to the Sertoli cells within the seminiferous tubules to promote spermatogenesis. FSH also stimulates the Sertoli cells to produce hormones called inhibins, which function to inhibit FSH release from the pituitary, thus reducing testosterone secretion. These polypeptide hormones correlate directly with Sertoli cell function and sperm number; inhibin B can be used as a marker of spermatogenic activity. In men, LH binds to receptors on Leydig cells in the testes and upregulates the production of testosterone.

A negative feedback loop predominantly controls the synthesis and secretion of both FSH and LH. Low blood concentrations of testosterone stimulate the hypothalamic release of GnRH. GnRH then stimulates the anterior pituitary to secrete LH into the bloodstream. In the testis, LH binds to LH receptors on Leydig cells and stimulates the release of testosterone. When concentrations of testosterone in the blood reach a critical threshold, testosterone itself will bind to androgen receptors on both the hypothalamus and the anterior pituitary, inhibiting the synthesis and secretion of GnRH and LH, respectively. When the blood concentrations of testosterone once again decline, testosterone no longer interacts with the receptors to the same degree and GnRH and LH are once again secreted, stimulating more testosterone production. This same process occurs with FSH and inhibin to control spermatogenesis.


### Male Reproductive System

Declines in Leydig cell activity can occur in men beginning at 40 to 50 years of age. The resulting reduction in circulating testosterone concentrations can lead to symptoms of andropause, also known as male menopause. While the reduction in sex steroids in men is akin to female menopause, there is no clear sign—such as a lack of a menstrual period—to denote the initiation of andropause. Instead, men report feelings of fatigue, reduced muscle mass, depression, anxiety, irritability, loss of libido, and insomnia. A reduction in spermatogenesis resulting in lowered fertility is also reported, and sexual dysfunction can also be associated with andropausal symptoms.

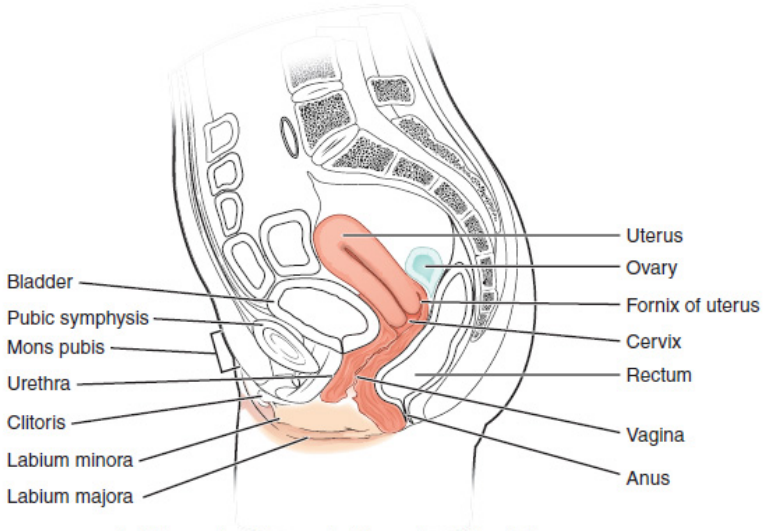
Whereas some researchers believe that certain aspects of andropause are difficult to tease apart from aging in general, testosterone replacement is sometimes prescribed to alleviate some symptoms. Recent studies have shown a benefit from androgen replacement therapy on the new onset of depression in elderly men; however, other studies caution against testosterone replacement for long-term treatment of andropause symptoms, showing that high doses can sharply increase the risk of both heart disease and prostate cancer.

## 27.2 | Anatomy and Physiology of the Female Reproductive System

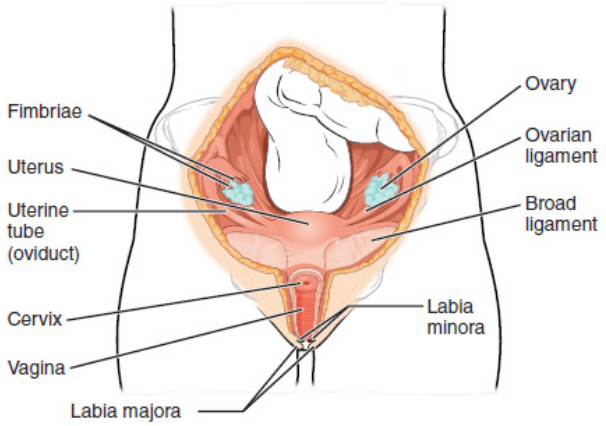
By the end of this section, you will be able to:

- Describe the structure and function of the organs of the female reproductive system
- List the steps of oogenesis
- Describe the hormonal changes that occur during the ovarian and menstrual cycles
- Trace the path of an oocyte from ovary to fertilization

The female reproductive system functions to produce gametes and reproductive hormones, just like the male reproductive system; however, it also has the additional task of supporting the developing fetus and delivering it to the outside world. Unlike its male counterpart, the female reproductive system is located primarily inside the pelvic cavity (**Figure 27.9**). Recall that the ovaries are the female gonads. The gamete they produce is called an **oocyte**. We'll discuss the production of oocytes in detail shortly. First, let's look at some of the structures of the female reproductive system.




(a) Human female reproductive system: lateral view




(b) Human female reproductive system: anterior view

**Figure 27.9 Female Reproductive System** The major organs of the female reproductive system are located inside the pelvic cavity.

## External Female Genitals

The external female reproductive structures are referred to collectively as the **vulva** (Figure 27.10). The **mons pubis** is a pad of fat that is located at the anterior, over the pubic bone. After puberty, it becomes covered in pubic hair. The **labia majora** (labia = "lips"; majora = "larger") are folds of hair-covered skin that begin just posterior to the mons pubis. The thinner and more pigmented **labia minora** (labia = "lips"; minora = "smaller") extend medial to the labia majora. Although they naturally vary in shape and size from woman to woman, the labia minora serve to protect the female urethra and the entrance to the female reproductive tract.

The superior, anterior portions of the labia minora come together to encircle the **clitoris** (or glans clitoris), an organ that originates from the same cells as the glans penis and has abundant nerves that make it important in sexual sensation and orgasm. The **hymen** is a thin membrane that sometimes partially covers the entrance to the vagina. An intact hymen cannot be used as an indication of "virginity"; even at birth, this is only a partial membrane, as menstrual fluid and other secretions must be able to exit the body, regardless of penile–vaginal intercourse. The vaginal opening is located between the opening of the urethra and the anus. It is flanked by outlets to the **Bartholin's glands** (or greater vestibular glands).

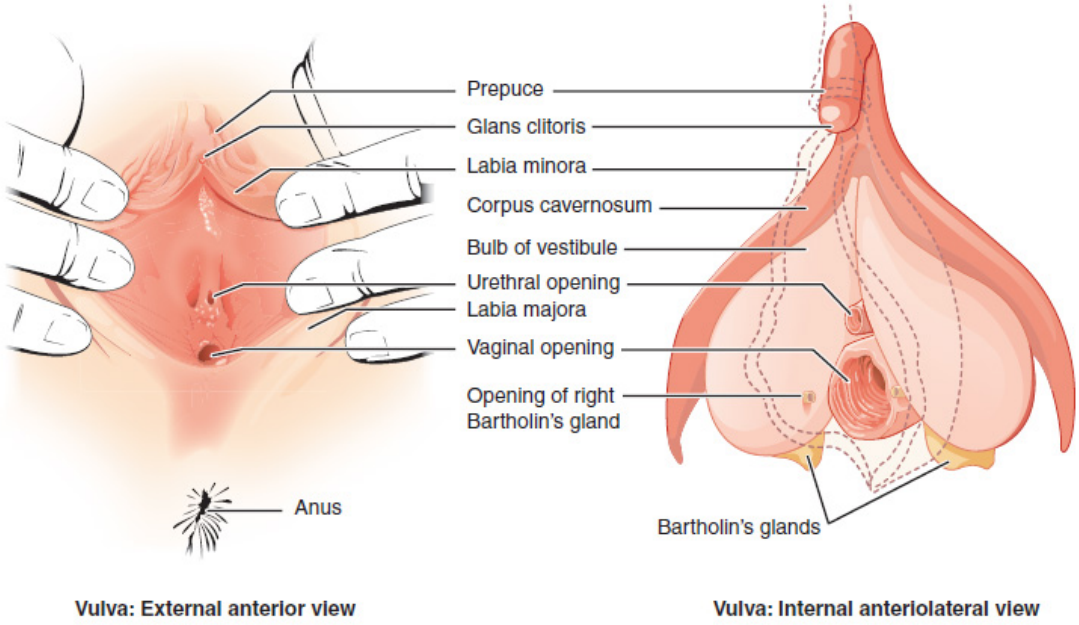



**Figure 27.10 The Vulva** The external female genitalia are referred to collectively as the vulva.

## Vagina

The **vagina**, shown at the bottom of **Figure 27.9** and **Figure 27.9**, is a muscular canal (approximately 10 cm long) that serves as the entrance to the reproductive tract. It also serves as the exit from the uterus during menses and childbirth. The outer walls of the anterior and posterior vagina are formed into longitudinal columns, or ridges, and the superior portion of the vagina—called the fornix—meets the protruding uterine cervix. The walls of the vagina are lined with an outer, fibrous adventitia; a middle layer of smooth muscle; and an inner mucous membrane with transverse folds called **rugae**. Together, the middle and inner layers allow the expansion of the vagina to accommodate intercourse and childbirth. The thin, perforated hymen can partially surround the opening to the vaginal orifice. The hymen can be ruptured with strenuous physical exercise, penile–vaginal intercourse, and childbirth. The Bartholin's glands and the lesser vestibular glands (located near the clitoris) secrete mucus, which keeps the vestibular area moist.

The vagina is home to a normal population of microorganisms that help to protect against infection by pathogenic bacteria, yeast, or other organisms that can enter the vagina. In a healthy woman, the most predominant type of vaginal bacteria is from the genus *Lactobacillus*. This family of beneficial bacterial flora secretes lactic acid, and thus protects the vagina by maintaining an acidic pH (below 4.5). Potential pathogens are less likely to survive in these acidic conditions. Lactic acid, in combination with other vaginal secretions, makes the vagina a self-cleansing organ. However, douching—or washing out the vagina with fluid—can disrupt the normal balance of healthy microorganisms, and actually increase a woman's risk for infections and irritation. Indeed, the American College of Obstetricians and Gynecologists recommend that women do not douche, and that they allow the vagina to maintain its normal healthy population of protective microbial flora.

## Ovaries

The **ovaries** are the female gonads (see **Figure 27.9**). Paired ovals, they are each about 2 to 3 cm in length, about the size of an almond. The ovaries are located within the pelvic cavity, and are supported by the mesovarium, an extension of the peritoneum that connects the ovaries to the **broad ligament**. Extending from the mesovarium itself is the suspensory ligament that contains the ovarian blood and lymph vessels. Finally, the ovary itself is attached to the uterus via the ovarian ligament.

The ovary comprises an outer covering of cuboidal epithelium called the ovarian surface epithelium that is superficial to a dense connective tissue covering called the tunica albuginea. Beneath the tunica albuginea is the cortex, or outer portion, of the organ. The cortex is composed of a tissue framework called the ovarian stroma that forms the bulk of the adult ovary. Oocytes develop within the outer layer of this stroma, each surrounded by supporting cells. This grouping of an oocyte and its supporting cells is called a **follicle**. The growth and development of ovarian follicles will be described shortly. Beneath the cortex lies the inner ovarian medulla, the site of blood vessels, lymph vessels, and the nerves of the ovary. You will learn more about the overall anatomy of the female reproductive system at the end of this section.

## The Ovarian Cycle

The **ovarian cycle** is a set of predictable changes in a female's oocytes and ovarian follicles. During a woman's reproductive years, it is a roughly 28-day cycle that can be correlated with, but is not the same as, the menstrual cycle (discussed shortly). The cycle includes two interrelated processes: oogenesis (the production of female gametes) and folliculogenesis (the growth and development of ovarian follicles).

### Oogenesis

Gametogenesis in females is called **oogenesis**. The process begins with the ovarian stem cells, or **oogonia** (Figure 27.11). Oogonia are formed during fetal development, and divide via mitosis, much like spermatogonia in the testis. Unlike spermatogonia, however, oogonia form primary oocytes in the fetal ovary prior to birth. These primary oocytes are then arrested in this stage of meiosis I, only to resume it years later, beginning at puberty and continuing until the woman is near menopause (the cessation of a woman's reproductive functions). The number of primary oocytes present in the ovaries declines from one to two million in an infant, to approximately 400,000 at puberty, to zero by the end of menopause.

The initiation of **ovulation**—the release of an oocyte from the ovary—marks the transition from puberty into reproductive maturity for women. From then on, throughout a woman's reproductive years, ovulation occurs approximately once every 28 days. Just prior to ovulation, a surge of luteinizing hormone triggers the resumption of meiosis in a primary oocyte. This initiates the transition from primary to secondary oocyte. However, as you can see in Figure 27.11, this cell division does not result in two identical cells. Instead, the cytoplasm is divided unequally, and one daughter cell is much larger than the other. This larger cell, the secondary oocyte, eventually leaves the ovary during ovulation. The smaller cell, called the first **polar body**, may or may not complete meiosis and produce second polar bodies; in either case, it eventually disintegrates. Therefore, even though oogenesis produces up to four cells, only one survives.

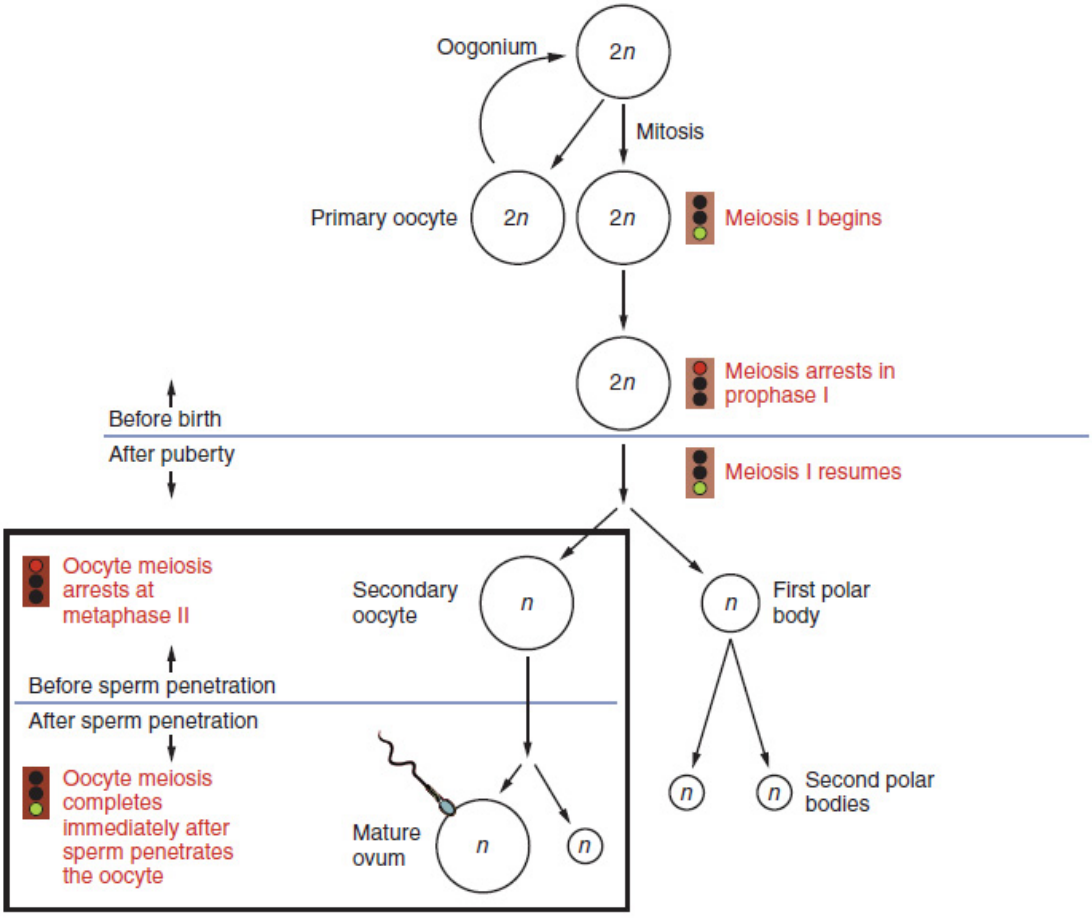



**Figure 27.11 Oogenesis** The unequal cell division of oogenesis produces one to three polar bodies that later degrade, as well as a single haploid ovum, which is produced only if there is penetration of the secondary oocyte by a sperm cell.

How does the diploid secondary oocyte become an **ovum**—the haploid female gamete? Meiosis of a secondary oocyte is completed only if a sperm succeeds in penetrating its barriers. Meiosis II then resumes, producing one haploid ovum that, at the instant of fertilization by a (haploid) sperm, becomes the first diploid cell of the new offspring (a zygote). Thus, the ovum can be thought of as a brief, transitional, haploid stage between the diploid oocyte and diploid zygote.

The larger amount of cytoplasm contained in the female gamete is used to supply the developing zygote with nutrients during the period between fertilization and implantation into the uterus. Interestingly, sperm contribute only DNA at fertilization —not cytoplasm. Therefore, the cytoplasm and all of the cytoplasmic organelles in the developing embryo are of maternal origin. This includes mitochondria, which contain their own DNA. Scientific research in the 1980s determined that mitochondrial DNA was maternally inherited, meaning that you can trace your mitochondrial DNA directly to your mother, her mother, and so on back through your female ancestors.

Everyday CONNECTION

## Mapping Human History with Mitochondrial DNA

When we talk about human DNA, we're usually referring to nuclear DNA; that is, the DNA coiled into chromosomal bundles in the nucleus of our cells. We inherit half of our nuclear DNA from our father, and half from our mother. However, mitochondrial DNA (mtDNA) comes only from the mitochondria in the cytoplasm of the fat ovum we inherit from our mother. She received her mtDNA from her mother, who got it from her mother, and so on. Each of our cells contains approximately 1700 mitochondria, with each mitochondrion packed with mtDNA containing approximately 37 genes.

Mutations (changes) in mtDNA occur spontaneously in a somewhat organized pattern at regular intervals in human history. By analyzing these mutational relationships, researchers have been able to determine that we can all trace our ancestry back to one woman who lived in Africa about 200,000 years ago. Scientists have given this woman the biblical name Eve, although she is not, of course, the first *Homo sapiens* female. More precisely, she is our most recent common ancestor through matrilineal descent.

This doesn't mean that everyone's mtDNA today looks exactly like that of our ancestral Eve. Because of the spontaneous mutations in mtDNA that have occurred over the centuries, researchers can map different "branches" off of the "main trunk" of our mtDNA family tree. Your mtDNA might have a pattern of mutations that aligns more closely with one branch, and your neighbor's may align with another branch. Still, all branches eventually lead back to Eve.

But what happened to the mtDNA of all of the other *Homo sapiens* females who were living at the time of Eve? Researchers explain that, over the centuries, their female descendants died childless or with only male children, and thus, their maternal line—and its mtDNA—ended.

### Folliculogenesis

Again, ovarian follicles are oocytes and their supporting cells. They grow and develop in a process called **folliculogenesis**, which typically leads to ovulation of one follicle approximately every 28 days, along with death to multiple other follicles. The death of ovarian follicles is called atresia, and can occur at any point during follicular development. Recall that, a female infant at birth will have one to two million oocytes within her ovarian follicles, and that this number declines throughout life until menopause, when no follicles remain. As you'll see next, follicles progress from primordial, to primary, to secondary and tertiary stages prior to ovulation—with the oocyte inside the follicle remaining as a primary oocyte until right before ovulation.

Folliculogenesis begins with follicles in a resting state. These small **primordial follicles** are present in newborn females and are the prevailing follicle type in the adult ovary (Figure 27.12). Primordial follicles have only a single flat layer of support cells, called **granulosa cells**, that surround the oocyte, and they can stay in this resting state for years—some until right before menopause.

After puberty, a few primordial follicles will respond to a recruitment signal each day, and will join a pool of immature growing follicles called **primary follicles**. Primary follicles start with a single layer of granulosa cells, but the granulosa cells then become active and transition from a flat or squamous shape to a rounded, cuboidal shape as they increase in size and proliferate. As the granulosa cells divide, the follicles—now called **secondary follicles** (see Figure 27.12)—increase in diameter, adding a new outer layer of connective tissue, blood vessels, and **theca cells**—cells that work with the granulosa cells to produce estrogens.

Within the growing secondary follicle, the primary oocyte now secretes a thin acellular membrane called the zona pellucida that will play a critical role in fertilization. A thick fluid, called follicular fluid, that has formed between the granulosa cells also begins to collect into one large pool, or **antrum**. Follicles in which the antrum has become large and fully formed are considered **tertiary follicles** (or antral follicles). Several follicles reach the tertiary stage at the same time, and most of these will undergo atresia. The one that does not die will continue to grow and develop until ovulation, when it will expel its secondary oocyte surrounded by several layers of granulosa cells from the ovary. Keep in mind that most follicles don't make it to this point. In fact, roughly 99 percent of the follicles in the ovary will undergo atresia, which can occur at any stage of folliculogenesis.

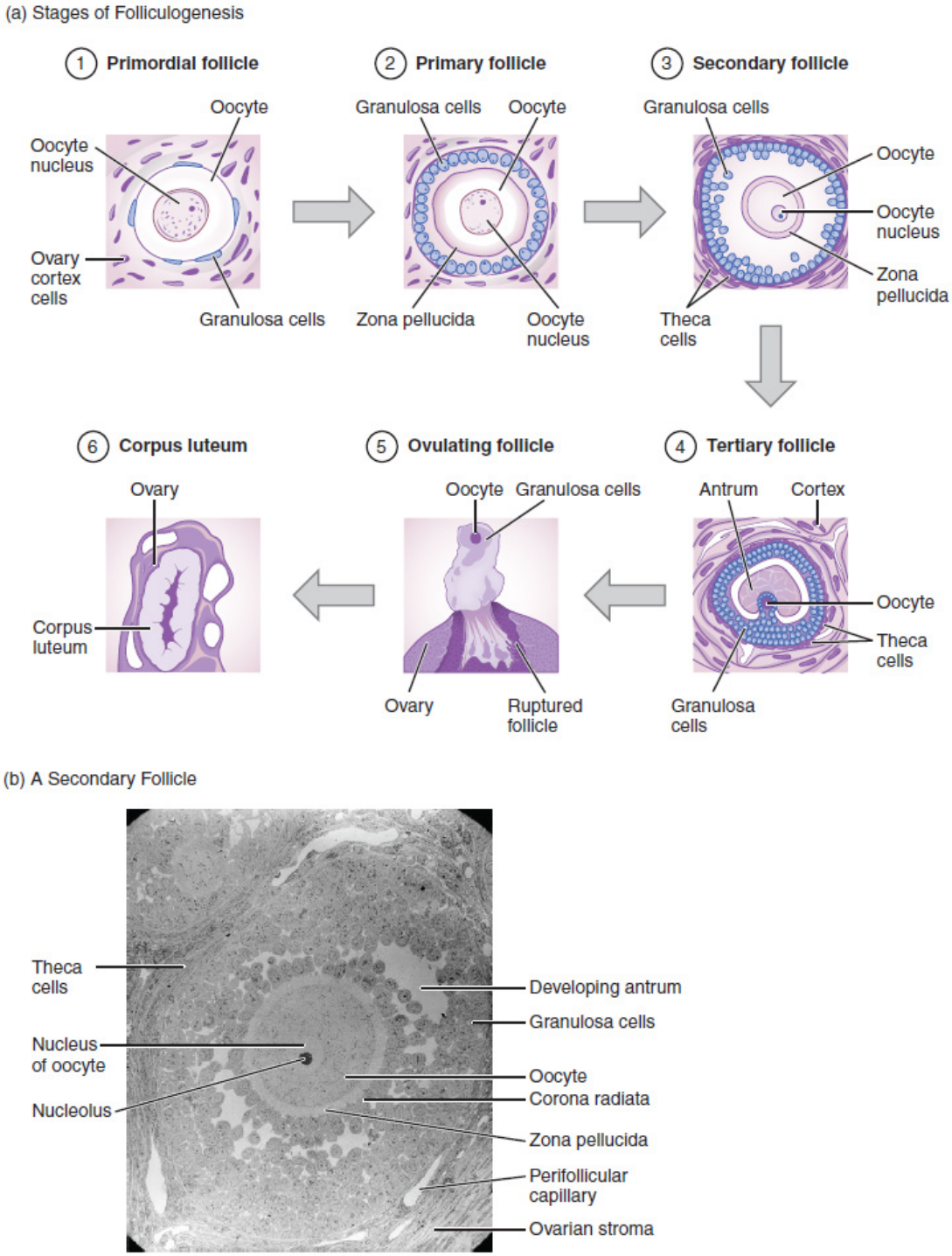



**Figure 27.12 Folliculogenesis** (a) The maturation of a follicle is shown in a clockwise direction proceeding from the primordial follicles. FSH stimulates the growth of a tertiary follicle, and LH stimulates the production of estrogen by granulosa and theca cells. Once the follicle is mature, it ruptures and releases the oocyte. Cells remaining in the follicle then develop into the corpus luteum. (b) In this electron micrograph of a secondary follicle, the oocyte, theca cells (thecae folliculi), and developing antrum are clearly visible. EM × 1100. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

## Hormonal Control of the Ovarian Cycle

The process of development that we have just described, from primordial follicle to early tertiary follicle, takes approximately two months in humans. The final stages of development of a small cohort of tertiary follicles, ending with ovulation of a secondary oocyte, occur over a course of approximately 28 days. These changes are regulated by many of the same hormones that regulate the male reproductive system, including GnRH, LH, and FSH.

As in men, the hypothalamus produces GnRH, a hormone that signals the anterior pituitary gland to produce the gonadotropins FSH and LH (**Figure 27.13**). These gonadotropins leave the pituitary and travel through the bloodstream to the ovaries, where they bind to receptors on the granulosa and theca cells of the follicles. FSH stimulates the follicles to grow (hence its name of follicle-stimulating hormone), and the five or six tertiary follicles expand in diameter. The release of LH also stimulates the granulosa and theca cells of the follicles to produce the sex steroid hormone estradiol, a type of estrogen. This phase of the ovarian cycle, when the tertiary follicles are growing and secreting estrogen, is known as the follicular phase.

The more granulosa and theca cells a follicle has (that is, the larger and more developed it is), the more estrogen it will produce in response to LH stimulation. As a result of these large follicles producing large amounts of estrogen, systemic plasma estrogen concentrations increase. Following a classic negative feedback loop, the high concentrations of estrogen will stimulate the hypothalamus and pituitary to reduce the production of GnRH, LH, and FSH. Because the large tertiary follicles require FSH to grow and survive at this point, this decline in FSH caused by negative feedback leads most of them to die (atresia). Typically only one follicle, now called the dominant follicle, will survive this reduction in FSH, and this follicle will be the one that releases an oocyte. Scientists have studied many factors that lead to a particular follicle becoming dominant: size, the number of granulosa cells, and the number of FSH receptors on those granulosa cells all contribute to a follicle becoming the one surviving dominant follicle.

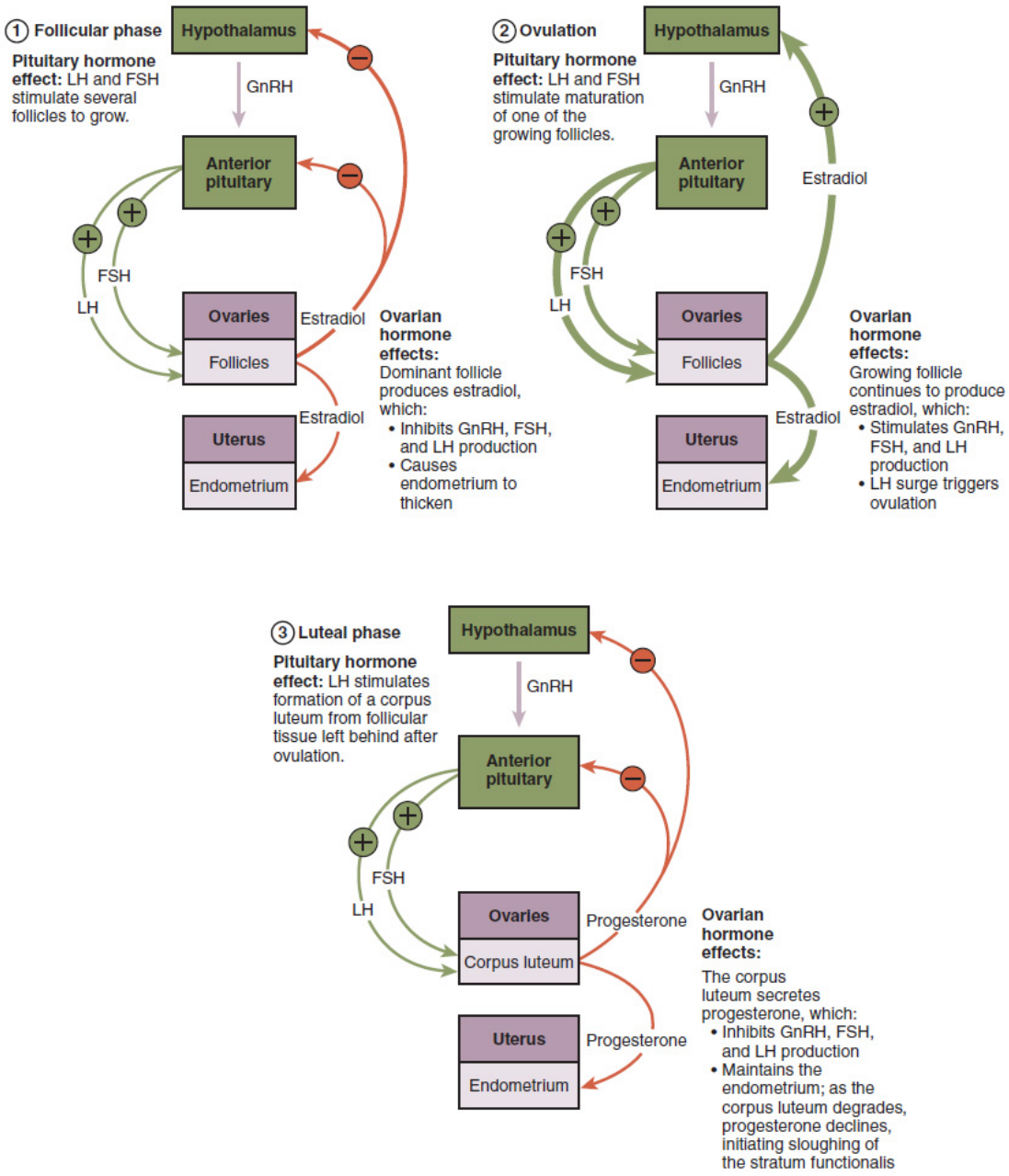



**Figure 27.13 Hormonal Regulation of Ovulation** The hypothalamus and pituitary gland regulate the ovarian cycle and ovulation. GnRH activates the anterior pituitary to produce LH and FSH, which stimulate the production of estrogen and progesterone by the ovaries.

When only the one dominant follicle remains in the ovary, it again begins to secrete estrogen. It produces more estrogen than all of the developing follicles did together before the negative feedback occurred. It produces so much estrogen that the normal negative feedback doesn't occur. Instead, these extremely high concentrations of systemic plasma estrogen trigger a regulatory switch in the anterior pituitary that responds by secreting large amounts of LH and FSH into the bloodstream (see Figure 27.13). The positive feedback loop by which more estrogen triggers release of more LH and FSH only occurs at this point in the cycle.

It is this large burst of LH (called the LH surge) that leads to ovulation of the dominant follicle. The LH surge induces many changes in the dominant follicle, including stimulating the resumption of meiosis of the primary oocyte to a secondary oocyte. As noted earlier, the polar body that results from unequal cell division simply degrades. The LH surge also triggers proteases (enzymes that cleave proteins) to break down structural proteins in the ovary wall on the surface of the bulging dominant follicle. This degradation of the wall, combined with pressure from the large, fluid-filled antrum, results in the expulsion of the oocyte surrounded by granulosa cells into the peritoneal cavity. This release is ovulation.

In the next section, you will follow the ovulated oocyte as it travels toward the uterus, but there is one more important event that occurs in the ovarian cycle. The surge of LH also stimulates a change in the granulosa and theca cells that remain in the follicle after the oocyte has been ovulated. This change is called luteinization (recall that the full name of LH is

luteinizing hormone), and it transforms the collapsed follicle into a new endocrine structure called the **corpus luteum**, a term meaning "yellowish body" (see **Figure 27.12**). Instead of estrogen, the luteinized granulosa and theca cells of the corpus luteum begin to produce large amounts of the sex steroid hormone progesterone, a hormone that is critical for the establishment and maintenance of pregnancy. Progesterone triggers negative feedback at the hypothalamus and pituitary, which keeps GnRH, LH, and FSH secretions low, so no new dominant follicles develop at this time.

The post-ovulatory phase of progesterone secretion is known as the luteal phase of the ovarian cycle. If pregnancy does not occur within 10 to 12 days, the corpus luteum will stop secreting progesterone and degrade into the **corpus albicans**, a nonfunctional "whitish body" that will disintegrate in the ovary over a period of several months. During this time of reduced progesterone secretion, FSH and LH are once again stimulated, and the follicular phase begins again with a new cohort of early tertiary follicles beginning to grow and secrete estrogen.

## The Uterine Tubes

The **uterine tubes** (also called fallopian tubes or oviducts) serve as the conduit of the oocyte from the ovary to the uterus (**Figure 27.14**). Each of the two uterine tubes is close to, but not directly connected to, the ovary and divided into sections. The **isthmus** is the narrow medial end of each uterine tube that is connected to the uterus. The wide distal **infundibulum** flares out with slender, finger-like projections called **fimbriae**. The middle region of the tube, called the **ampulla**, is where fertilization often occurs. The uterine tubes also have three layers: an outer serosa, a middle smooth muscle layer, and an inner mucosal layer. In addition to its mucus-secreting cells, the inner mucosa contains ciliated cells that beat in the direction of the uterus, producing a current that will be critical to move the oocyte.

Following ovulation, the secondary oocyte surrounded by a few granulosa cells is released into the peritoneal cavity. The nearby uterine tube, either left or right, receives the oocyte. Unlike sperm, oocytes lack flagella, and therefore cannot move on their own. So how do they travel into the uterine tube and toward the uterus? High concentrations of estrogen that occur around the time of ovulation induce contractions of the smooth muscle along the length of the uterine tube. These contractions occur every 4 to 8 seconds, and the result is a coordinated movement that sweeps the surface of the ovary and the pelvic cavity. Current flowing toward the uterus is generated by coordinated beating of the cilia that line the outside and lumen of the length of the uterine tube. These cilia beat more strongly in response to the high estrogen concentrations that occur around the time of ovulation. As a result of these mechanisms, the oocyte–granulosa cell complex is pulled into the interior of the tube. Once inside, the muscular contractions and beating cilia move the oocyte slowly toward the uterus. When fertilization does occur, sperm typically meet the egg while it is still moving through the ampulla.



Watch this **video (http://openstaxcollege.org/l/ovulation)** to observe ovulation and its initiation in response to the release of FSH and LH from the pituitary gland. What specialized structures help guide the oocyte from the ovary into the uterine tube?

If the oocyte is successfully fertilized, the resulting zygote will begin to divide into two cells, then four, and so on, as it makes its way through the uterine tube and into the uterus. There, it will implant and continue to grow. If the egg is not fertilized, it will simply degrade—either in the uterine tube or in the uterus, where it may be shed with the next menstrual period.

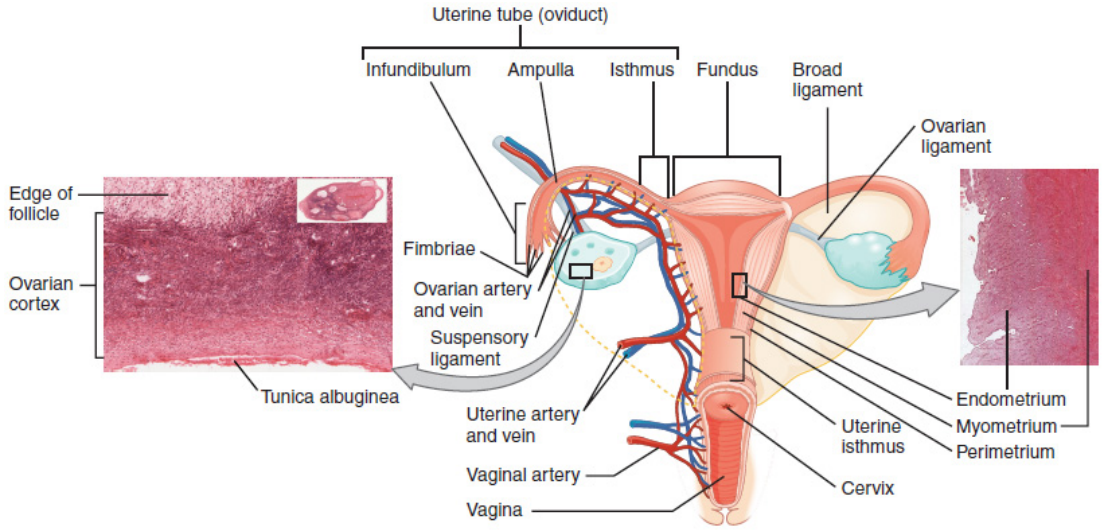



**Figure 27.14 Ovaries, Uterine Tubes, and Uterus** This anterior view shows the relationship of the ovaries, uterine tubes (oviducts), and uterus. Sperm enter through the vagina, and fertilization of an ovulated oocyte usually occurs in the distal uterine tube. From left to right, LM × 400, LM × 20. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

The open-ended structure of the uterine tubes can have significant health consequences if bacteria or other contagions enter through the vagina and move through the uterus, into the tubes, and then into the pelvic cavity. If this is left unchecked, a bacterial infection (sepsis) could quickly become life-threatening. The spread of an infection in this manner is of special concern when unskilled practitioners perform abortions in non-sterile conditions. Sepsis is also associated with sexually transmitted bacterial infections, especially gonorrhea and chlamydia. These increase a woman's risk for pelvic inflammatory disease (PID), infection of the uterine tubes or other reproductive organs. Even when resolved, PID can leave scar tissue in the tubes, leading to infertility.

## Interactive LINK

Watch this series of **videos (http://openstaxcollege.org/l/oocyte)** to look at the movement of the oocyte through the ovary. The cilia in the uterine tube promote movement of the oocyte. What would likely occur if the cilia were paralyzed at the time of ovulation?

## The Uterus and Cervix

The **uterus** is the muscular organ that nourishes and supports the growing embryo (see **Figure 27.14**). Its average size is approximately 5 cm wide by 7 cm long (approximately 2 in by 3 in) when a female is not pregnant. It has three sections. The portion of the uterus superior to the opening of the uterine tubes is called the **fundus**. The middle section of the uterus is called the **body of uterus** (or corpus). The **cervix** is the narrow inferior portion of the uterus that projects into the vagina. The cervix produces mucus secretions that become thin and stringy under the influence of high systemic plasma estrogen concentrations, and these secretions can facilitate sperm movement through the reproductive tract.

Several ligaments maintain the position of the uterus within the abdominopelvic cavity. The broad ligament is a fold of peritoneum that serves as a primary support for the uterus, extending laterally from both sides of the uterus and attaching it to the pelvic wall. The round ligament attaches to the uterus near the uterine tubes, and extends to the labia majora. Finally, the uterosacral ligament stabilizes the uterus posteriorly by its connection from the cervix to the pelvic wall.

The wall of the uterus is made up of three layers. The most superficial layer is the serous membrane, or **perimetrium**, which consists of epithelial tissue that covers the exterior portion of the uterus. The middle layer, or **myometrium**, is a thick layer of smooth muscle responsible for uterine contractions. Most of the uterus is myometrial tissue, and the muscle fibers run horizontally, vertically, and diagonally, allowing the powerful contractions that occur during labor and the less powerful contractions (or cramps) that help to expel menstrual blood during a woman's period. Anteriorly directed myometrial contractions also occur near the time of ovulation, and are thought to possibly facilitate the transport of sperm through the female reproductive tract.

The innermost layer of the uterus is called the **endometrium**. The endometrium contains a connective tissue lining, the lamina propria, which is covered by epithelial tissue that lines the lumen. Structurally, the endometrium consists of two layers: the stratum basalis and the stratum functionalis (the basal and functional layers). The stratum basalis layer is part of the lamina propria and is adjacent to the myometrium; this layer does not shed during menses. In contrast, the thicker stratum functionalis layer contains the glandular portion of the lamina propria and the endothelial tissue that lines the uterine lumen. It is the stratum functionalis that grows and thickens in response to increased levels of estrogen and progesterone. In the luteal phase of the menstrual cycle, special branches off of the uterine artery called spiral arteries supply the thickened stratum functionalis. This inner functional layer provides the proper site of implantation for the fertilized egg, and—should fertilization not occur—it is only the stratum functionalis layer of the endometrium that sheds during menstruation.

Recall that during the follicular phase of the ovarian cycle, the tertiary follicles are growing and secreting estrogen. At the same time, the stratum functionalis of the endometrium is thickening to prepare for a potential implantation. The post-ovulatory increase in progesterone, which characterizes the luteal phase, is key for maintaining a thick stratum functionalis. As long as a functional corpus luteum is present in the ovary, the endometrial lining is prepared for implantation. Indeed, if an embryo implants, signals are sent to the corpus luteum to continue secreting progesterone to maintain the endometrium, and thus maintain the pregnancy. If an embryo does not implant, no signal is sent to the corpus luteum and it degrades, ceasing progesterone production and ending the luteal phase. Without progesterone, the endometrium thins and, under the influence of prostaglandins, the spiral arteries of the endometrium constrict and rupture, preventing oxygenated blood from reaching the endometrial tissue. As a result, endometrial tissue dies and blood, pieces of the endometrial tissue, and white blood cells are shed through the vagina during menstruation, or the **menses**. The first menses after puberty, called **menarche**, can occur either before or after the first ovulation.

## The Menstrual Cycle

Now that we have discussed the maturation of the cohort of tertiary follicles in the ovary, the build-up and then shedding of the endometrial lining in the uterus, and the function of the uterine tubes and vagina, we can put everything together to talk about the three phases of the **menstrual cycle**—the series of changes in which the uterine lining is shed, rebuilds, and prepares for implantation.

The timing of the menstrual cycle starts with the first day of menses, referred to as day one of a woman's period. Cycle length is determined by counting the days between the onset of bleeding in two subsequent cycles. Because the average length of a woman's menstrual cycle is 28 days, this is the time period used to identify the timing of events in the cycle. However, the length of the menstrual cycle varies among women, and even in the same woman from one cycle to the next, typically from 21 to 32 days.

Just as the hormones produced by the granulosa and theca cells of the ovary "drive" the follicular and luteal phases of the ovarian cycle, they also control the three distinct phases of the menstrual cycle. These are the menses phase, the proliferative phase, and the secretory phase.

### Menses Phase

The **menses phase** of the menstrual cycle is the phase during which the lining is shed; that is, the days that the woman menstruates. Although it averages approximately five days, the menses phase can last from 2 to 7 days, or longer. As shown in **Figure 27.15**, the menses phase occurs during the early days of the follicular phase of the ovarian cycle, when progesterone, FSH, and LH levels are low. Recall that progesterone concentrations decline as a result of the degradation of the corpus luteum, marking the end of the luteal phase. This decline in progesterone triggers the shedding of the stratum functionalis of the endometrium.

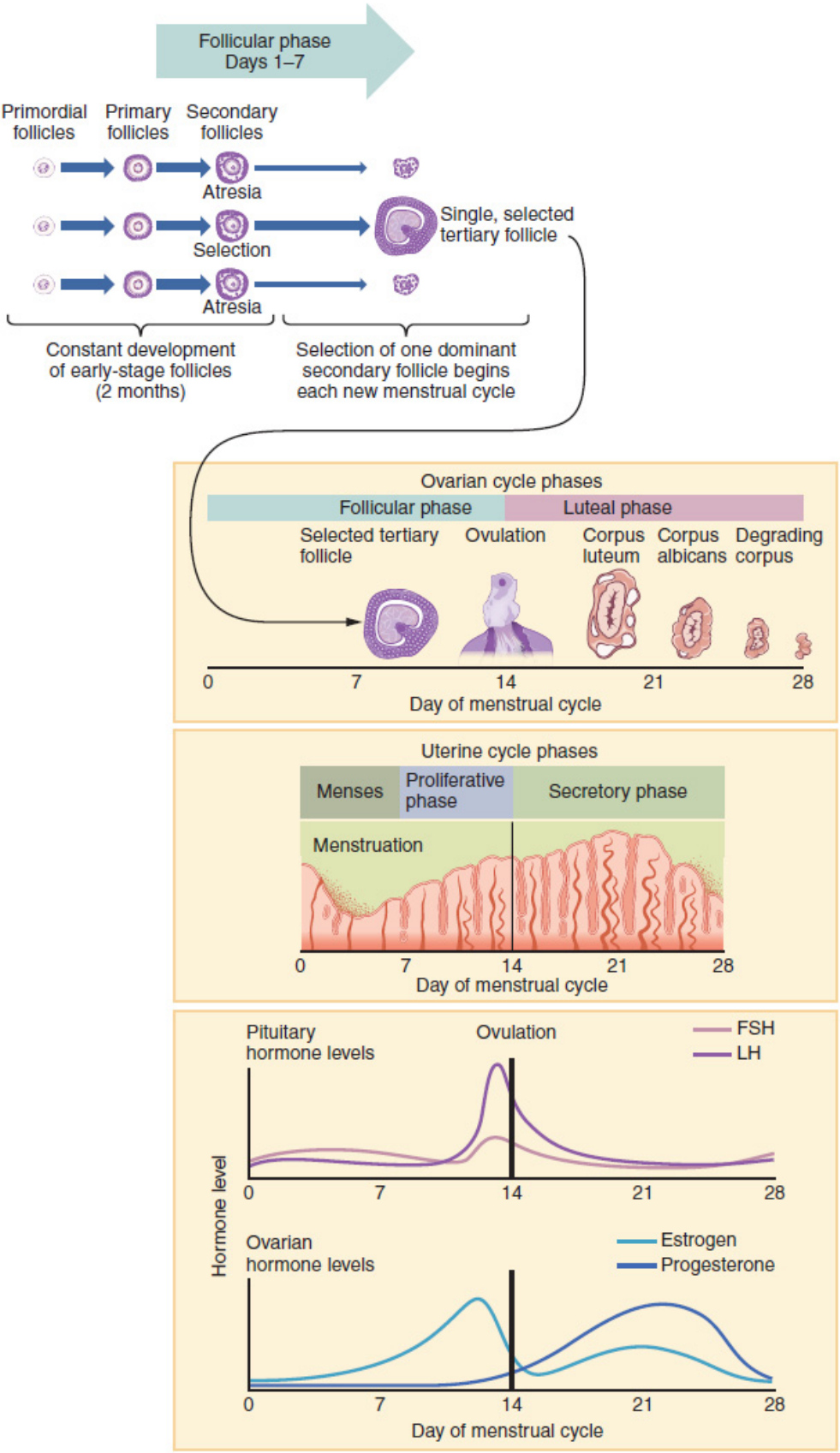



**Figure 27.15 Hormone Levels in Ovarian and Menstrual Cycles** The correlation of the hormone levels and their effects on the female reproductive system is shown in this timeline of the ovarian and menstrual cycles. The menstrual cycle begins at day one with the start of menses. Ovulation occurs around day 14 of a 28-day cycle, triggered by the LH surge.

### Proliferative Phase

Once menstrual flow ceases, the endometrium begins to proliferate again, marking the beginning of the **proliferative phase** of the menstrual cycle (see **Figure 27.15**). It occurs when the granulosa and theca cells of the tertiary follicles begin to produce increased amounts of estrogen. These rising estrogen concentrations stimulate the endometrial lining to rebuild.

Recall that the high estrogen concentrations will eventually lead to a decrease in FSH as a result of negative feedback, resulting in atresia of all but one of the developing tertiary follicles. The switch to positive feedback—which occurs with the elevated estrogen production from the dominant follicle—then stimulates the LH surge that will trigger ovulation. In a typical 28-day menstrual cycle, ovulation occurs on day 14. Ovulation marks the end of the proliferative phase as well as the end of the follicular phase.

### Secretory Phase

In addition to prompting the LH surge, high estrogen levels increase the uterine tube contractions that facilitate the pick-up and transfer of the ovulated oocyte. High estrogen levels also slightly decrease the acidity of the vagina, making it more hospitable to sperm. In the ovary, the luteinization of the granulosa cells of the collapsed follicle forms the progesterone-producing corpus luteum, marking the beginning of the luteal phase of the ovarian cycle. In the uterus, progesterone from the corpus luteum begins the **secretory phase** of the menstrual cycle, in which the endometrial lining prepares for implantation (see **Figure 27.15**). Over the next 10 to 12 days, the endometrial glands secrete a fluid rich in glycogen. If fertilization has occurred, this fluid will nourish the ball of cells now developing from the zygote. At the same time, the spiral arteries develop to provide blood to the thickened stratum functionalis.

If no pregnancy occurs within approximately 10 to 12 days, the corpus luteum will degrade into the corpus albicans. Levels of both estrogen and progesterone will fall, and the endometrium will grow thinner. Prostaglandins will be secreted that cause constriction of the spiral arteries, reducing oxygen supply. The endometrial tissue will die, resulting in menses—or the first day of the next cycle.

Disorders OF THE...

## Female Reproductive System

Research over many years has confirmed that cervical cancer is most often caused by a sexually transmitted infection with human papillomavirus (HPV). There are over 100 related viruses in the HPV family, and the characteristics of each strain determine the outcome of the infection. In all cases, the virus enters body cells and uses its own genetic material to take over the host cell's metabolic machinery and produce more virus particles.

HPV infections are common in both men and women. Indeed, a recent study determined that 42.5 percent of females had HPV at the time of testing. These women ranged in age from 14 to 59 years and differed in race, ethnicity, and number of sexual partners. Of note, the prevalence of HPV infection was 53.8 percent among women aged 20 to 24 years, the age group with the highest infection rate.

HPV strains are classified as high or low risk according to their potential to cause cancer. Though most HPV infections do not cause disease, the disruption of normal cellular functions in the low-risk forms of HPV can cause the male or female human host to develop genital warts. Often, the body is able to clear an HPV infection by normal immune responses within 2 years. However, the more serious, high-risk infection by certain types of HPV can result in cancer of the cervix (**Figure 27.16**). Infection with either of the cancer-causing variants HPV 16 or HPV 18 has been linked to more than 70 percent of all cervical cancer diagnoses. Although even these high-risk HPV strains can be cleared from the body over time, infections persist in some individuals. If this happens, the HPV infection can influence the cells of the cervix to develop precancerous changes.

Risk factors for cervical cancer include having unprotected sex; having multiple sexual partners; a first sexual experience at a younger age, when the cells of the cervix are not fully mature; failure to receive the HPV vaccine; a compromised immune system; and smoking. The risk of developing cervical cancer is doubled with cigarette smoking.

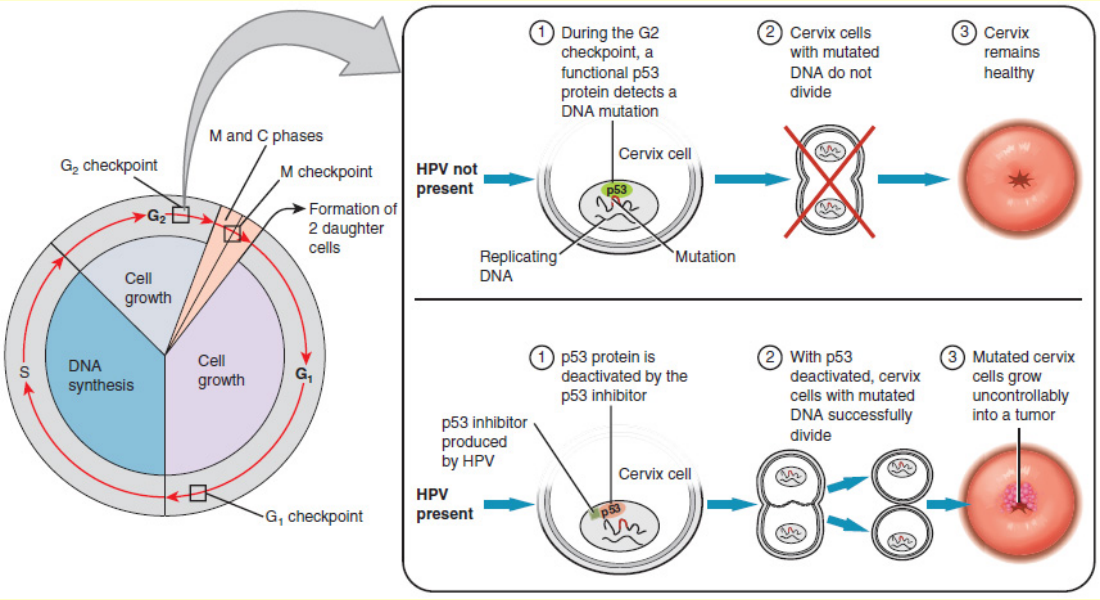



**Figure 27.16 Development of Cervical Cancer** In most cases, cells infected with the HPV virus heal on their own. In some cases, however, the virus continues to spread and becomes an invasive cancer.

When the high-risk types of HPV enter a cell, two viral proteins are used to neutralize proteins that the host cells use as checkpoints in the cell cycle. The best studied of these proteins is p53. In a normal cell, p53 detects DNA damage in the cell's genome and either halts the progression of the cell cycle—allowing time for DNA repair to occur—or initiates apoptosis. Both of these processes prevent the accumulation of mutations in a cell's genome. High-risk HPV can neutralize p53, keeping the cell in a state in which fast growth is possible and impairing apoptosis, allowing mutations to accumulate in the cellular DNA.

The prevalence of cervical cancer in the United States is very low because of regular screening exams called pap smears. Pap smears sample cells of the cervix, allowing the detection of abnormal cells. If pre-cancerous cells are detected, there are several highly effective techniques that are currently in use to remove them before they pose a danger. However, women in developing countries often do not have access to regular pap smears. As a result, these women account for as many as 80 percent of the cases of cervical cancer worldwide.

In 2006, the first vaccine against the high-risk types of HPV was approved. There are now two HPV vaccines available: Gardasil® and Cervarix®. Whereas these vaccines were initially only targeted for women, because HPV is

sexually transmitted, both men and women require vaccination for this approach to achieve its maximum efficacy. A recent study suggests that the HPV vaccine has cut the rates of HPV infection by the four targeted strains at least in half. Unfortunately, the high cost of manufacturing the vaccine is currently limiting access to many women worldwide.

## The Breasts

Whereas the breasts are located far from the other female reproductive organs, they are considered accessory organs of the female reproductive system. The function of the breasts is to supply milk to an infant in a process called lactation. The external features of the breast include a nipple surrounded by a pigmented **areola** (Figure 27.17), whose coloration may deepen during pregnancy. The areola is typically circular and can vary in size from 25 to 100 mm in diameter. The areolar region is characterized by small, raised areolar glands that secrete lubricating fluid during lactation to protect the nipple from chafing. When a baby nurses, or draws milk from the breast, the entire areolar region is taken into the mouth.

Breast milk is produced by the **mammary glands**, which are modified sweat glands. The milk itself exits the breast through the nipple via 15 to 20 **lactiferous ducts** that open on the surface of the nipple. These lactiferous ducts each extend to a **lactiferous sinus** that connects to a glandular lobe within the breast itself that contains groups of milk-secreting cells in clusters called **alveoli** (see Figure 27.17). The clusters can change in size depending on the amount of milk in the alveolar lumen. Once milk is made in the alveoli, stimulated myoepithelial cells that surround the alveoli contract to push the milk to the lactiferous sinuses. From here, the baby can draw milk through the lactiferous ducts by suckling. The lobes themselves are surrounded by fat tissue, which determines the size of the breast; breast size differs between individuals and does not affect the amount of milk produced. Supporting the breasts are multiple bands of connective tissue called **suspensory ligaments** that connect the breast tissue to the dermis of the overlying skin.

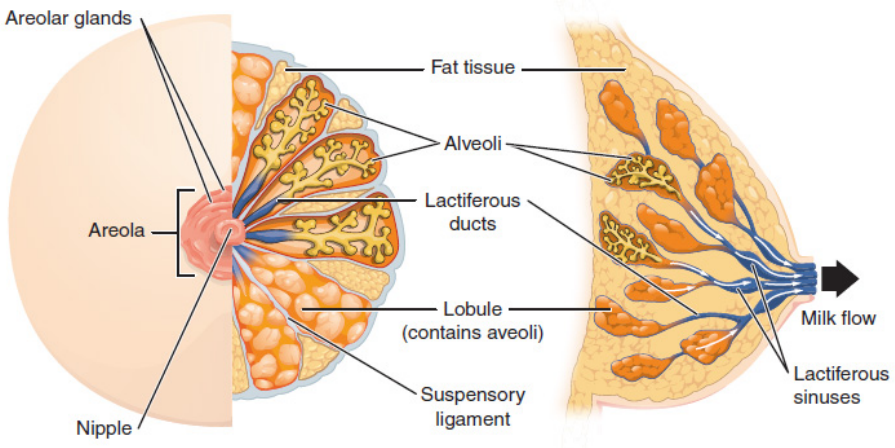



**Figure 27.17 Anatomy of the Breast** During lactation, milk moves from the alveoli through the lactiferous ducts to the nipple.

During the normal hormonal fluctuations in the menstrual cycle, breast tissue responds to changing levels of estrogen and progesterone, which can lead to swelling and breast tenderness in some individuals, especially during the secretory phase. If pregnancy occurs, the increase in hormones leads to further development of the mammary tissue and enlargement of the breasts.

## Hormonal Birth Control

Birth control pills take advantage of the negative feedback system that regulates the ovarian and menstrual cycles to stop ovulation and prevent pregnancy. Typically they work by providing a constant level of both estrogen and progesterone, which negatively feeds back onto the hypothalamus and pituitary, thus preventing the release of FSH and LH. Without FSH, the follicles do not mature, and without the LH surge, ovulation does not occur. Although the estrogen in birth control pills does stimulate some thickening of the endometrial wall, it is reduced compared with a normal cycle and is less likely to support implantation.

Some birth control pills contain 21 active pills containing hormones, and 7 inactive pills (placebos). The decline in hormones during the week that the woman takes the placebo pills triggers menses, although it is typically lighter than a normal menstrual flow because of the reduced endometrial thickening. Newer types of birth control pills have been developed that deliver low-dose estrogens and progesterone for the entire cycle (these are meant to be taken 365 days a year), and menses never occurs. While some women prefer to have the proof of a lack of pregnancy that a monthly period provides, menstruation every 28 days is not required for health reasons, and there are no reported adverse effects of not having a menstrual period in an otherwise healthy individual.

Because birth control pills function by providing constant estrogen and progesterone levels and disrupting negative feedback, skipping even just one or two pills at certain points of the cycle (or even being several hours late taking the

pill) can lead to an increase in FSH and LH and result in ovulation. It is important, therefore, that the woman follow the directions on the birth control pill package to successfully prevent pregnancy.

## Aging AND THE...

### Female Reproductive System

Female fertility (the ability to conceive) peaks when women are in their twenties, and is slowly reduced until a women reaches 35 years of age. After that time, fertility declines more rapidly, until it ends completely at the end of menopause. Menopause is the cessation of the menstrual cycle that occurs as a result of the loss of ovarian follicles and the hormones that they produce. A woman is considered to have completed menopause if she has not menstruated in a full year. After that point, she is considered postmenopausal. The average age for this change is consistent worldwide at between 50 and 52 years of age, but it can normally occur in a woman's forties, or later in her fifties. Poor health, including smoking, can lead to earlier loss of fertility and earlier menopause.

As a woman reaches the age of menopause, depletion of the number of viable follicles in the ovaries due to atresia affects the hormonal regulation of the menstrual cycle. During the years leading up to menopause, there is a decrease in the levels of the hormone inhibin, which normally participates in a negative feedback loop to the pituitary to control the production of FSH. The menopausal decrease in inhibin leads to an increase in FSH. The presence of FSH stimulates more follicles to grow and secrete estrogen. Because small, secondary follicles also respond to increases in FSH levels, larger numbers of follicles are stimulated to grow; however, most undergo atresia and die. Eventually, this process leads to the depletion of all follicles in the ovaries, and the production of estrogen falls off dramatically. It is primarily the lack of estrogens that leads to the symptoms of menopause.

The earliest changes occur during the menopausal transition, often referred to as peri-menopause, when a women's cycle becomes irregular but does not stop entirely. Although the levels of estrogen are still nearly the same as before the transition, the level of progesterone produced by the corpus luteum is reduced. This decline in progesterone can lead to abnormal growth, or hyperplasia, of the endometrium. This condition is a concern because it increases the risk of developing endometrial cancer. Two harmless conditions that can develop during the transition are uterine fibroids, which are benign masses of cells, and irregular bleeding. As estrogen levels change, other symptoms that occur are hot flashes and night sweats, trouble sleeping, vaginal dryness, mood swings, difficulty focusing, and thinning of hair on the head along with the growth of more hair on the face. Depending on the individual, these symptoms can be entirely absent, moderate, or severe.

After menopause, lower amounts of estrogens can lead to other changes. Cardiovascular disease becomes as prevalent in women as in men, possibly because estrogens reduce the amount of cholesterol in the blood vessels. When estrogen is lacking, many women find that they suddenly have problems with high cholesterol and the cardiovascular issues that accompany it. Osteoporosis is another problem because bone density decreases rapidly in the first years after menopause. The reduction in bone density leads to a higher incidence of fractures.

Hormone therapy (HT), which employs medication (synthetic estrogens and progestins) to increase estrogen and progestin levels, can alleviate some of the symptoms of menopause. In 2002, the Women's Health Initiative began a study to observe women for the long-term outcomes of hormone replacement therapy over 8.5 years. However, the study was prematurely terminated after 5.2 years because of evidence of a higher than normal risk of breast cancer in patients taking estrogen-only HT. The potential positive effects on cardiovascular disease were also not realized in the estrogen-only patients. The results of other hormone replacement studies over the last 50 years, including a 2012 study that followed over 1,000 menopausal women for 10 years, have shown cardiovascular benefits from estrogen and no increased risk for cancer. Some researchers believe that the age group tested in the 2002 trial may have been too old to benefit from the therapy, thus skewing the results. In the meantime, intense debate and study of the benefits and risks of replacement therapy is ongoing. Current guidelines approve HT for the reduction of hot flashes or flushes, but this treatment is generally only considered when women first start showing signs of menopausal changes, is used in the lowest dose possible for the shortest time possible (5 years or less), and it is suggested that women on HT have regular pelvic and breast exams.

## 27.3 | Development of the Male and Female Reproductive Systems

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

- Explain how bipotential tissues are directed to develop into male or female sex organs
- Name the rudimentary duct systems in the embryo that are precursors to male or female internal sex organs
- Describe the hormonal changes that bring about puberty, and the secondary sex characteristics of men and women

The development of the reproductive systems begins soon after fertilization of the egg, with primordial gonads beginning to develop approximately one month after conception. Reproductive development continues in utero, but there is little change in the reproductive system between infancy and puberty.

## Development of the Sexual Organs in the Embryo and Fetus

Females are considered the "fundamental" sex—that is, without much chemical prompting, all fertilized eggs would develop into females. To become a male, an individual must be exposed to the cascade of factors initiated by a single gene on the male Y chromosome. This is called the SRY (*S*ex-determining *R*egion of the *Y* chromosome). Because females do not have a Y chromosome, they do not have the *SRY* gene. Without a functional *SRY* gene, an individual will be female.

In both male and female embryos, the same group of cells has the potential to develop into either the male or female gonads; this tissue is considered bipotential. The *SRY* gene actively recruits other genes that begin to develop the testes, and suppresses genes that are important in female development. As part of this *SRY*-prompted cascade, germ cells in the bipotential gonads differentiate into spermatogonia. Without *SRY*, different genes are expressed, oogonia form, and primordial follicles develop in the primitive ovary.

Soon after the formation of the testis, the Leydig cells begin to secrete testosterone. Testosterone can influence tissues that are bipotential to become male reproductive structures. For example, with exposure to testosterone, cells that could become either the glans penis or the glans clitoris form the glans penis. Without testosterone, these same cells differentiate into the clitoris.

Not all tissues in the reproductive tract are bipotential. The internal reproductive structures (for example the uterus, uterine tubes, and part of the vagina in females; and the epididymis, ductus deferens, and seminal vesicles in males) form from one of two rudimentary duct systems in the embryo. For proper reproductive function in the adult, one set of these ducts must develop properly, and the other must degrade. In males, secretions from sustentacular cells trigger a degradation of the female duct, called the **Müllerian duct**. At the same time, testosterone secretion stimulates growth of the male tract, the **Wolffian duct**. Without such sustentacular cell secretion, the Müllerian duct will develop; without testosterone, the Wolffian duct will degrade. Thus, the developing offspring will be female. For more information and a figure of differentiation of the gonads, seek additional content on fetal development.



A baby's gender is determined at conception, and the different genitalia of male and female fetuses develop from the same tissues in the embryo. View this **animation (http://openstaxcollege.org/l/fetus)** to see a comparison of the development of structures of the female and male reproductive systems in a growing fetus. Where are the testes located for most of gestational time?

## Further Sexual Development Occurs at Puberty

**Puberty** is the stage of development at which individuals become sexually mature. Though the outcomes of puberty for boys and girls are very different, the hormonal control of the process is very similar. In addition, though the timing of these events varies between individuals, the sequence of changes that occur is predictable for male and female adolescents. As shown in **Figure 27.18**, a concerted release of hormones from the hypothalamus (GnRH), the anterior pituitary (LH and FSH), and the gonads (either testosterone or estrogen) is responsible for the maturation of the reproductive systems and the development of **secondary sex characteristics**, which are physical changes that serve auxiliary roles in reproduction.

The first changes begin around the age of eight or nine when the production of LH becomes detectable. The release of LH occurs primarily at night during sleep and precedes the physical changes of puberty by several years. In pre-pubertal children, the sensitivity of the negative feedback system in the hypothalamus and pituitary is very high. This means that very low concentrations of androgens or estrogens will negatively feed back onto the hypothalamus and pituitary, keeping the production of GnRH, LH, and FSH low.

As an individual approaches puberty, two changes in sensitivity occur. The first is a decrease of sensitivity in the hypothalamus and pituitary to negative feedback, meaning that it takes increasingly larger concentrations of sex steroid hormones to stop the production of LH and FSH. The second change in sensitivity is an increase in sensitivity of the

gonads to the FSH and LH signals, meaning the gonads of adults are more responsive to gonadotropins than are the gonads of children. As a result of these two changes, the levels of LH and FSH slowly increase and lead to the enlargement and maturation of the gonads, which in turn leads to secretion of higher levels of sex hormones and the initiation of spermatogenesis and folliculogenesis.

In addition to age, multiple factors can affect the age of onset of puberty, including genetics, environment, and psychological stress. One of the more important influences may be nutrition; historical data demonstrate the effect of better and more consistent nutrition on the age of menarche in girls in the United States, which decreased from an average age of approximately 17 years of age in 1860 to the current age of approximately 12.75 years in 1960, as it remains today. Some studies indicate a link between puberty onset and the amount of stored fat in an individual. This effect is more pronounced in girls, but has been documented in both sexes. Body fat, corresponding with secretion of the hormone leptin by adipose cells, appears to have a strong role in determining menarche. This may reflect to some extent the high metabolic costs of gestation and lactation. In girls who are lean and highly active, such as gymnasts, there is often a delay in the onset of puberty.

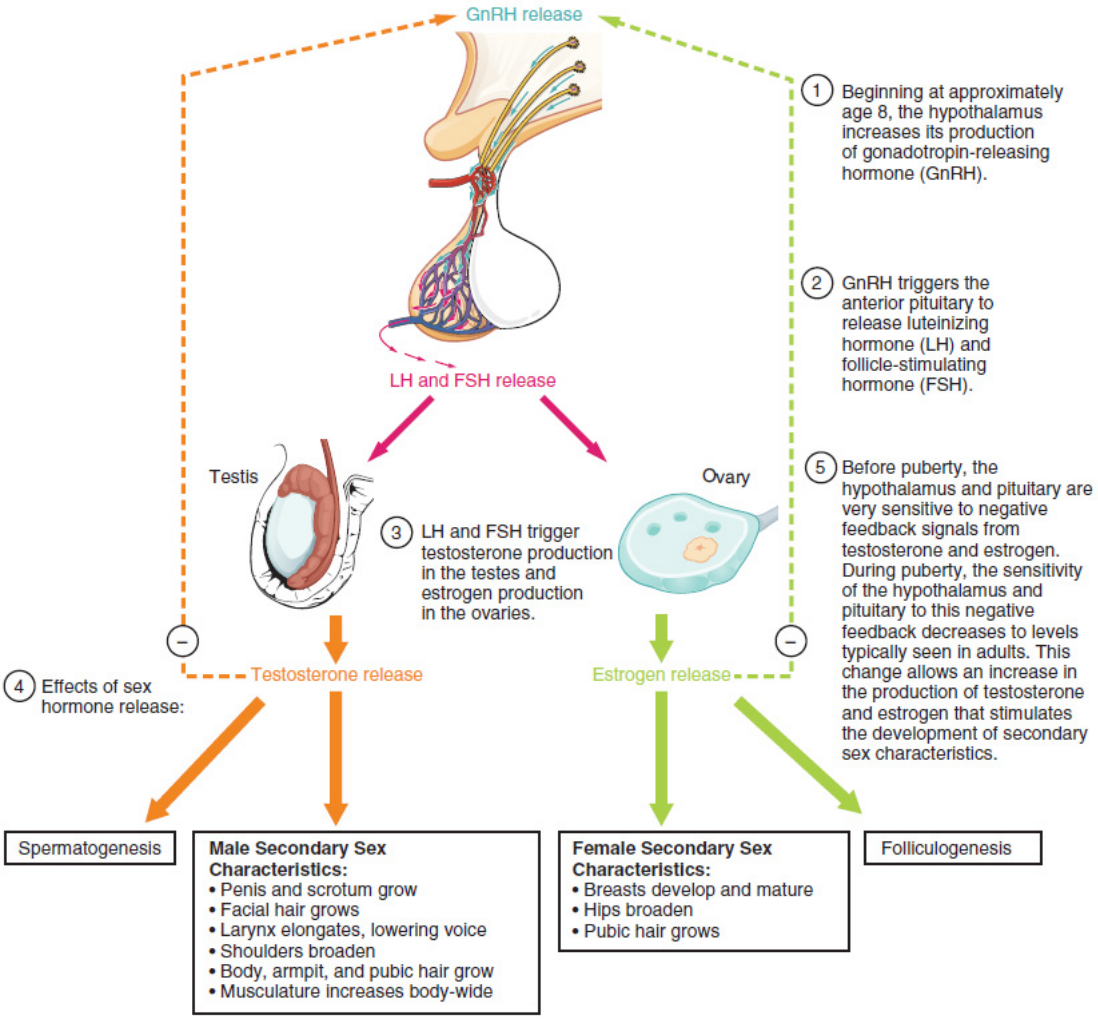



**Figure 27.18 Hormones of Puberty** During puberty, the release of LH and FSH from the anterior pituitary stimulates the gonads to produce sex hormones in both male and female adolescents.

## Signs of Puberty

Different sex steroid hormone concentrations between the sexes also contribute to the development and function of secondary sexual characteristics. Examples of secondary sexual characteristics are listed in **Table 27.1**.

## Development of the Secondary Sexual Characteristics

| Male | Female |
|---|---|
| Increased larynx size and deepening of the voice | Deposition of fat, predominantly in breasts and hips |
| Increased muscular development | Breast development |
| Growth of facial, axillary, and pubic hair, and increased growth of body hair | Broadening of the pelvis and growth of axillary and pubic hair |

**Table 27.1**

As a girl reaches puberty, typically the first change that is visible is the development of the breast tissue. This is followed by the growth of axillary and pubic hair. A growth spurt normally starts at approximately age 9 to 11, and may last two years or more. During this time, a girl's height can increase 3 inches a year. The next step in puberty is menarche, the start of menstruation.

In boys, the growth of the testes is typically the first physical sign of the beginning of puberty, which is followed by growth and pigmentation of the scrotum and growth of the penis. The next step is the growth of hair, including armpit, pubic, chest, and facial hair. Testosterone stimulates the growth of the larynx and thickening and lengthening of the vocal folds, which causes the voice to drop in pitch. The first fertile ejaculations typically appear at approximately 15 years of age, but this age can vary widely across individual boys. Unlike the early growth spurt observed in females, the male growth spurt occurs toward the end of puberty, at approximately age 11 to 13, and a boy's height can increase as much as 4 inches a year. In some males, pubertal development can continue through the early 20s.

## KEY TERMS

**alveoli** (of the breast) milk-secreting cells in the mammary gland

**ampulla** (of the uterine tube) middle portion of the uterine tube in which fertilization often occurs

**antrum** fluid-filled chamber that characterizes a mature tertiary (antral) follicle

**areola** highly pigmented, circular area surrounding the raised nipple and containing areolar glands that secrete fluid important for lubrication during suckling

**Bartholin's glands** (also, greater vestibular glands) glands that produce a thick mucus that maintains moisture in the vulva area; also referred to as the greater vestibular glands

**blood–testis barrier** tight junctions between Sertoli cells that prevent bloodborne pathogens from gaining access to later stages of spermatogenesis and prevent the potential for an autoimmune reaction to haploid sperm

**body of uterus** middle section of the uterus

**broad ligament** wide ligament that supports the uterus by attaching laterally to both sides of the uterus and pelvic wall

**bulbourethral glands** (also, Cowper's glands) glands that secrete a lubricating mucus that cleans and lubricates the urethra prior to and during ejaculation

**cervix** elongate inferior end of the uterus where it connects to the vagina

**clitoris** (also, glans clitoris) nerve-rich area of the vulva that contributes to sexual sensation during intercourse

**corpus albicans** nonfunctional structure remaining in the ovarian stroma following structural and functional regression of the corpus luteum

**corpus cavernosum** either of two columns of erectile tissue in the penis that fill with blood during an erection

**corpus luteum** transformed follicle after ovulation that secretes progesterone

**corpus spongiosum** (plural = corpora cavernosa) column of erectile tissue in the penis that fills with blood during an erection and surrounds the penile urethra on the ventral portion of the penis

**ductus deferens** (also, vas deferens) duct that transports sperm from the epididymis through the spermatic cord and into the ejaculatory duct; also referred as the vas deferens

**ejaculatory duct** duct that connects the ampulla of the ductus deferens with the duct of the seminal vesicle at the prostatic urethra

**endometrium** inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses

**epididymis** (plural = epididymides) coiled tubular structure in which sperm start to mature and are stored until ejaculation

**fimbriae** fingerlike projections on the distal uterine tubes

**follicle** ovarian structure of one oocyte and surrounding granulosa (and later theca) cells

**folliculogenesis** development of ovarian follicles from primordial to tertiary under the stimulation of gonadotropins

**fundus** (of the uterus) domed portion of the uterus that is superior to the uterine tubes

**gamete** haploid reproductive cell that contributes genetic material to form an offspring

**glans penis** bulbous end of the penis that contains a large number of nerve endings

**gonadotropin-releasing hormone (GnRH)** hormone released by the hypothalamus that regulates the production of follicle-stimulating hormone and luteinizing hormone from the pituitary gland

**gonads** reproductive organs (testes in men and ovaries in women) that produce gametes and reproductive hormones

**granulosa cells** supportive cells in the ovarian follicle that produce estrogen

**hymen** membrane that covers part of the opening of the vagina

**infundibulum** (of the uterine tube) wide, distal portion of the uterine tube terminating in fimbriae

**inguinal canal** opening in abdominal wall that connects the testes to the abdominal cavity

**isthmus** narrow, medial portion of the uterine tube that joins the uterus

**Leydig cells** cells between the seminiferous tubules of the testes that produce testosterone; a type of interstitial cell

**labia majora** hair-covered folds of skin located behind the mons pubis

**labia minora** thin, pigmented, hairless flaps of skin located medial and deep to the labia majora

**lactiferous ducts** ducts that connect the mammary glands to the nipple and allow for the transport of milk

**lactiferous sinus** area of milk collection between alveoli and lactiferous duct

**Müllerian duct** duct system present in the embryo that will eventually form the internal female reproductive structures

**mammary glands** glands inside the breast that secrete milk

**menarche** first menstruation in a pubertal female

**menses phase** phase of the menstrual cycle in which the endometrial lining is shed

**menses** shedding of the inner portion of the endometrium out though the vagina; also referred to as menstruation

**menstrual cycle** approximately 28-day cycle of changes in the uterus consisting of a menses phase, a proliferative phase, and a secretory phase

**mons pubis** mound of fatty tissue located at the front of the vulva

**myometrium** smooth muscle layer of uterus that allows for uterine contractions during labor and expulsion of menstrual blood

**oocyte** cell that results from the division of the oogonium and undergoes meiosis I at the LH surge and meiosis II at fertilization to become a haploid ovum

**oogenesis** process by which oogonia divide by mitosis to primary oocytes, which undergo meiosis to produce the secondary oocyte and, upon fertilization, the ovum

**oogonia** ovarian stem cells that undergo mitosis during female fetal development to form primary oocytes

**ovarian cycle** approximately 28-day cycle of changes in the ovary consisting of a follicular phase and a luteal phase

**ovaries** female gonads that produce oocytes and sex steroid hormones (notably estrogen and progesterone)

**ovulation** release of a secondary oocyte and associated granulosa cells from an ovary

**ovum** haploid female gamete resulting from completion of meiosis II at fertilization

**penis** male organ of copulation

**perimetrium** outer epithelial layer of uterine wall

**polar body** smaller cell produced during the process of meiosis in oogenesis

**prepuce** (also, foreskin) flap of skin that forms a collar around, and thus protects and lubricates, the glans penis; also referred as the foreskin

**primary follicles** ovarian follicles with a primary oocyte and one layer of cuboidal granulosa cells

**primordial follicles** least developed ovarian follicles that consist of a single oocyte and a single layer of flat (squamous) granulosa cells

**proliferative phase** phase of the menstrual cycle in which the endometrium proliferates

**prostate gland** doughnut-shaped gland at the base of the bladder surrounding the urethra and contributing fluid to semen during ejaculation

**puberty** life stage during which a male or female adolescent becomes anatomically and physiologically capable of reproduction

**rugae** (of the vagina) folds of skin in the vagina that allow it to stretch during intercourse and childbirth

**Sertoli cells** cells that support germ cells through the process of spermatogenesis; a type of sustentacular cell

**scrotum** external pouch of skin and muscle that houses the testes

**secondary follicles** ovarian follicles with a primary oocyte and multiple layers of granulosa cells

**secondary sex characteristics** physical characteristics that are influenced by sex steroid hormones and have supporting roles in reproductive function

**secretory phase** phase of the menstrual cycle in which the endometrium secretes a nutrient-rich fluid in preparation for implantation of an embryo

**semen** ejaculatory fluid composed of sperm and secretions from the seminal vesicles, prostate, and bulbourethral glands

**seminal vesicle** gland that produces seminal fluid, which contributes to semen

**seminiferous tubules** tube structures within the testes where spermatogenesis occurs

**spermatic cord** bundle of nerves and blood vessels that supplies the testes; contains ductus deferens

**spermatid** immature sperm cells produced by meiosis II of secondary spermatocytes

**spermatocyte** cell that results from the division of spermatogonium and undergoes meiosis I and meiosis II to form spermatids

**spermatogenesis** formation of new sperm, occurs in the seminiferous tubules of the testes

**spermatogonia** (singular = spermatogonium) diploid precursor cells that become sperm

**spermiogenesis** transformation of spermatids to spermatozoa during spermatogenesis

**sperm** (also, spermatozoon) male gamete

**suspensory ligaments** bands of connective tissue that suspend the breast onto the chest wall by attachment to the overlying dermis

**tertiary follicles** (also, antral follicles) ovarian follicles with a primary or secondary oocyte, multiple layers of granulosa cells, and a fully formed antrum

**testes** (singular = testis) male gonads

**theca cells** estrogen-producing cells in a maturing ovarian follicle

**uterine tubes** (also, fallopian tubes or oviducts) ducts that facilitate transport of an ovulated oocyte to the uterus

**uterus** muscular hollow organ in which a fertilized egg develops into a fetus

**vagina** tunnel-like organ that provides access to the uterus for the insertion of semen and from the uterus for the birth of a baby

**vulva** external female genitalia

**Wolffian duct** duct system present in the embryo that will eventually form the internal male reproductive structures

# CHAPTER REVIEW

## 27.1 Anatomy and Physiology of the Male Reproductive System

Gametes are the reproductive cells that combine to form offspring. Organs called gonads produce the gametes, along with the hormones that regulate human reproduction. The male gametes are called sperm. Spermatogenesis, the production of sperm, occurs within the seminiferous tubules that make up most of the testis. The scrotum is the muscular sac that holds the testes outside of the body cavity.

Spermatogenesis begins with mitotic division of spermatogonia (stem cells) to produce primary spermatocytes that undergo the two divisions of meiosis to become secondary spermatocytes, then the haploid spermatids. During spermiogenesis, spermatids are transformed into spermatozoa (formed sperm). Upon release from the seminiferous tubules, sperm are moved to the epididymis where they continue to mature. During ejaculation, sperm exit the epididymis through the ductus deferens, a duct in the spermatic cord that leaves the scrotum. The ampulla of the ductus deferens meets the seminal vesicle, a gland that contributes fructose and proteins, at the ejaculatory duct. The fluid continues through the prostatic urethra, where secretions from the prostate are added to form semen. These secretions help the sperm to travel through the urethra and into the female reproductive tract. Secretions from the bulbourethral glands protect sperm and cleanse and lubricate the penile (spongy) urethra.

The penis is the male organ of copulation. Columns of erectile tissue called the corpora cavernosa and corpus spongiosum fill with blood when sexual arousal activates vasodilatation in the blood vessels of the penis. Testosterone regulates and maintains the sex organs and sex drive, and induces the physical changes of puberty. Interplay between the testes and the endocrine system precisely control the production of testosterone with a negative feedback loop.

## 27.2 Anatomy and Physiology of the Female Reproductive System

The external female genitalia are collectively called the vulva. The vagina is the pathway into and out of the uterus. The man’s penis is inserted into the vagina to deliver sperm, and the baby exits the uterus through the vagina during childbirth.

The ovaries produce oocytes, the female gametes, in a process called oogenesis. As with spermatogenesis, meiosis produces the haploid gamete (in this case, an ovum); however, it is completed only in an oocyte that has been penetrated by a sperm. In the ovary, an oocyte surrounded by supporting cells is called a follicle. In folliculogenesis, primordial follicles develop into primary, secondary, and tertiary follicles. Early tertiary follicles with their fluid-filled antrum will be stimulated by an increase in FSH, a gonadotropin produced by the anterior pituitary, to grow in the 28-day ovarian cycle. Supporting granulosa and theca cells in the growing follicles produce estrogens, until the level of estrogen in the bloodstream is high enough that it triggers negative feedback at the hypothalamus and pituitary. This results in a reduction of FSH and LH, and most tertiary follicles in the ovary undergo atresia (they die). One follicle, usually the one with the most FSH receptors, survives this period and is now called the dominant follicle. The dominant follicle produces more estrogen, triggering positive feedback and the LH surge that will induce ovulation. Following ovulation, the granulosa cells of the empty follicle luteinize and transform into the progesterone-producing corpus luteum. The ovulated oocyte with its surrounding granulosa cells is picked up by the infundibulum of the uterine tube, and beating cilia help to transport it through the tube toward the uterus. Fertilization occurs within the uterine tube, and the final stage of meiosis is completed.

The uterus has three regions: the fundus, the body, and the cervix. It has three layers: the outer perimetrium, the muscular myometrium, and the inner endometrium. The endometrium responds to estrogen released by the follicles during the menstrual cycle and grows thicker with an increase in blood vessels in preparation for pregnancy. If the egg is not fertilized, no signal is sent to extend the life of the corpus luteum, and it degrades, stopping progesterone production. This decline in progesterone results in the sloughing of the inner portion of the endometrium in a process called menses, or menstruation.

The breasts are accessory sexual organs that are utilized after the birth of a child to produce milk in a process called lactation. Birth control pills provide constant levels of estrogen and progesterone to negatively feed back on the hypothalamus and pituitary, and suppress the release of FSH and LH, which inhibits ovulation and prevents pregnancy.

## 27.3 Development of the Male and Female Reproductive Systems

The reproductive systems of males and females begin to develop soon after conception. A gene on the male’s Y chromosome called *SRY* is critical in stimulating a cascade of events that simultaneously stimulate testis development and repress the development of female structures. Testosterone produced by Leydig cells in the embryonic testis stimulates the development of male sexual organs. If testosterone is not present, female sexual organs will develop.

Whereas the gonads and some other reproductive tissues are considered bipotential, the tissue that forms the internal reproductive structures stems from ducts that will develop into only male (Wolffian) or female (Müllerian) structures. To be able to reproduce as an adult, one of these systems must develop properly and the other must degrade.

Further development of the reproductive systems occurs at puberty. The initiation of the changes that occur in puberty is the result of a decrease in sensitivity to negative feedback in the hypothalamus and pituitary gland, and an increase in sensitivity of the gonads to FSH and LH stimulation. These changes lead to increases in either estrogen or testosterone, in female and male adolescents, respectively. The increase in sex steroid hormones leads to maturation of the gonads and other

reproductive organs. The initiation of spermatogenesis begins in boys, and girls begin ovulating and menstruating. Increases in sex steroid hormones also lead to the development of secondary sex characteristics such as breast development in girls and facial hair and larynx growth in boys.

## INTERACTIVE LINK QUESTIONS

**1.** Watch this **video (http://openstaxcollege.org/l/vasectomy)** to learn about vasectomy. As described in this video, a vasectomy is a procedure in which a small section of the ductus (vas) deferens is removed from the scrotum. This interrupts the path taken by sperm through the ductus deferens. If sperm do not exit through the vas, either because the man has had a vasectomy or has not ejaculated, in what region of the testis do they remain?

**2.** Watch this **video (http://openstaxcollege.org/l/spermpath)** to explore the structures of the male reproductive system and the path of sperm that starts in the testes and ends as the sperm leave the penis through the urethra. Where are sperm deposited after they leave the ejaculatory duct?

**3.** Watch this **video (http://openstaxcollege.org/l/ovulation)** to observe ovulation and its initiation in response to the release of FSH and LH from the pituitary gland. What specialized structures help guide the oocyte from the ovary into the uterine tube?

**4.** Watch this series of **videos (http://openstaxcollege.org/l/oocyte)** to look at the movement of the oocyte through the ovary. The cilia in the uterine tube promote movement of the oocyte. What would likely occur if the cilia were paralyzed at the time of ovulation?

**5.** A baby's gender is determined at conception, and the different genitalia of male and female fetuses develop from the same tissues in the embryo. View this **animation (http://openstaxcollege.org/l/fetus)** that compares the development of structures of the female and male reproductive systems in a growing fetus. Where are the testes located for most of gestational time?

## REVIEW QUESTIONS

**6.** What are male gametes called?
- a. ova
- b. sperm
- c. testes
- d. testosterone

**7.** Leydig cells _____.
- a. secrete testosterone
- b. activate the sperm flagellum
- c. support spermatogenesis
- d. secrete seminal fluid

**8.** Which hypothalamic hormone contributes to the regulation of the male reproductive system?
- a. luteinizing hormone
- b. gonadotropin-releasing hormone
- c. follicle-stimulating hormone
- d. androgens

**9.** What is the function of the epididymis?
- a. sperm maturation and storage
- b. produces the bulk of seminal fluid
- c. provides nitric oxide needed for erections
- d. spermatogenesis

**10.** Spermatogenesis takes place in the _____.
- a. prostate gland
- b. glans penis
- c. seminiferous tubules
- d. ejaculatory duct

**11.** What are the female gonads called?
- a. oocytes
- b. ova
- c. oviducts
- d. ovaries

**12.** When do the oogonia undergo mitosis?
- a. before birth
- b. at puberty
- c. at the beginning of each menstrual cycle
- d. during fertilization

**13.** From what structure does the corpus luteum originate?
- a. uterine corpus
- b. dominant follicle
- c. fallopian tube
- d. corpus albicans

**14.** Where does fertilization of the egg by the sperm typically occur?
- a. vagina
- b. uterus
- c. uterine tube
- d. ovary

**15.** Why do estrogen levels fall after menopause?
- a. The ovaries degrade.
- b. There are no follicles left to produce estrogen.
- c. The pituitary secretes a menopause-specific hormone.
- d. The cells of the endometrium degenerate.

**16.** The vulva includes the _____.
- a. lactiferous duct, rugae, and hymen
- b. lactiferous duct, endometrium, and bulbourethral glands
- c. mons pubis, endometrium, and hymen
- d. mons pubis, labia majora, and Bartholin's glands

**17.** What controls whether an embryo will develop testes or ovaries?
- a. pituitary gland
- b. hypothalamus
- c. Y chromosome
- d. presence or absence of estrogen

**18.** Without *SRY* expression, an embryo will develop _____.

a. male reproductive structures
b. female reproductive structures
c. no reproductive structures
d. male reproductive structures 50 percent of the time and female reproductive structures 50 percent of the time

**19.** The timing of puberty can be influenced by which of the following?

a. genes
b. stress
c. amount of body fat
d. all of the above

## CRITICAL THINKING QUESTIONS

**20.** Briefly explain why mature gametes carry only one set of chromosomes.

**21.** What special features are evident in sperm cells but not in somatic cells, and how do these specializations function?

**22.** What do each of the three male accessory glands contribute to the semen?

**23.** Describe how penile erection occurs.

**24.** While anabolic steroids (synthetic testosterone) bulk up muscles, they can also affect testosterone production in the testis. Using what you know about negative feedback, describe what would happen to testosterone production in the testis if a male takes large amounts of synthetic testosterone.

**25.** Follow the path of ejaculated sperm from the vagina to the oocyte. Include all structures of the female reproductive tract that the sperm must swim through to reach the egg.

**26.** Identify some differences between meiosis in men and women.

**27.** Explain the hormonal regulation of the phases of the menstrual cycle.

**28.** Endometriosis is a disorder in which endometrial cells implant and proliferate outside of the uterus—in the uterine tubes, on the ovaries, or even in the pelvic cavity. Offer a theory as to why endometriosis increases a woman's risk of infertility.

**29.** Identify the changes in sensitivity that occur in the hypothalamus, pituitary, and gonads as a boy or girl approaches puberty. Explain how these changes lead to the increases of sex steroid hormone secretions that drive many pubertal changes.

**30.** Explain how the internal female and male reproductive structures develop from two different duct systems.

**31.** Explain what would occur during fetal development to an XY individual with a mutation causing a nonfunctional *SRY* gene.

# 28 | DEVELOPMENT AND INHERITANCE

**Figure 28.1 Newborn** A single fertilized egg develops over the span of nine months into an infant consisting of trillions of cells and capable of surviving outside the womb. (credit: “Seattleye”/flickr.com)

## Introduction

### Chapter Objectives

After studying this chapter, you will be able to:

- List and explain the steps involved in fertilization
- Describe the major events in embryonic development
- Describe the major events in fetal development
- Discuss the adaptations of a woman’s body to pregnancy
- Describe the physiologic adjustments that the newborn must make in the first hours of extrauterine life
- Summarize the physiology of lactation
- Classify and describe the different patterns of inheritance

In approximately nine months, a single cell—a fertilized egg—develops into a fully formed infant consisting of trillions of cells with myriad specialized functions. The dramatic changes of fertilization, embryonic development, and fetal development are followed by remarkable adaptations of the newborn to life outside the womb. An offspring's normal development depends upon the appropriate synthesis of structural and functional proteins. This, in turn, is governed by the genetic material inherited from the parental egg and sperm, as well as environmental factors.

# 28.1 | Fertilization

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

- Describe the obstacles that sperm must overcome to reach an oocyte
- Explain capacitation and its importance in fertilization
- Summarize the events that occur as a sperm fertilizes an oocyte

**Fertilization** occurs when a sperm and an oocyte (egg) combine and their nuclei fuse. Because each of these reproductive cells is a haploid cell containing half of the genetic material needed to form a human being, their combination forms a diploid cell. This new single cell, called a **zygote**, contains all of the genetic material needed to form a human—half from the mother and half from the father.

## Transit of Sperm

Fertilization is a numbers game. During ejaculation, hundreds of millions of sperm (spermatozoa) are released into the vagina. Almost immediately, millions of these sperm are overcome by the acidity of the vagina (approximately pH 3.8), and millions more may be blocked from entering the uterus by thick cervical mucus. Of those that do enter, thousands are destroyed by phagocytic uterine leukocytes. Thus, the race into the uterine tubes, which is the most typical site for sperm to encounter the oocyte, is reduced to a few thousand contenders. Their journey—thought to be facilitated by uterine contractions—usually takes from 30 minutes to 2 hours. If the sperm do not encounter an oocyte immediately, they can survive in the uterine tubes for another 3–5 days. Thus, fertilization can still occur if intercourse takes place a few days before ovulation. In comparison, an oocyte can survive independently for only approximately 24 hours following ovulation. Intercourse more than a day after ovulation will therefore usually not result in fertilization.

During the journey, fluids in the female reproductive tract prepare the sperm for fertilization through a process called **capacitation**, or priming. The fluids improve the motility of the spermatozoa. They also deplete cholesterol molecules embedded in the membrane of the head of the sperm, thinning the membrane in such a way that will help facilitate the release of the lysosomal (digestive) enzymes needed for the sperm to penetrate the oocyte's exterior once contact is made. Sperm must undergo the process of capacitation in order to have the "capacity" to fertilize an oocyte. If they reach the oocyte before capacitation is complete, they will be unable to penetrate the oocyte's thick outer layer of cells.

## Contact Between Sperm and Oocyte

Upon ovulation, the oocyte released by the ovary is swept into—and along—the uterine tube. Fertilization must occur in the distal uterine tube because an unfertilized oocyte cannot survive the 72-hour journey to the uterus. As you will recall from your study of the oogenesis, this oocyte (specifically a secondary oocyte) is surrounded by two protective layers. The **corona radiata** is an outer layer of follicular (granulosa) cells that form around a developing oocyte in the ovary and remain with it upon ovulation. The underlying **zona pellucida** (pellucid = "transparent") is a transparent, but thick, glycoprotein membrane that surrounds the cell's plasma membrane.

As it is swept along the distal uterine tube, the oocyte encounters the surviving capacitated sperm, which stream toward it in response to chemical attractants released by the cells of the corona radiata. To reach the oocyte itself, the sperm must penetrate the two protective layers. The sperm first burrow through the cells of the corona radiata. Then, upon contact with the zona pellucida, the sperm bind to receptors in the zona pellucida. This initiates a process called the **acrosomal reaction** in which the enzyme-filled "cap" of the sperm, called the **acrosome**, releases its stored digestive enzymes. These enzymes clear a path through the zona pellucida that allows sperm to reach the oocyte. Finally, a single sperm makes contact with sperm-binding receptors on the oocyte's plasma membrane (**Figure 28.2**). The plasma membrane of that sperm then fuses with the oocyte's plasma membrane, and the head and mid-piece of the "winning" sperm enter the oocyte interior.

How do sperm penetrate the corona radiata? Some sperm undergo a spontaneous acrosomal reaction, which is an acrosomal reaction not triggered by contact with the zona pellucida. The digestive enzymes released by this reaction digest the extracellular matrix of the corona radiata. As you can see, the first sperm to reach the oocyte is never the one to fertilize it. Rather, hundreds of sperm cells must undergo the acrosomal reaction, each helping to degrade the corona radiata and zona pellucida until a path is created to allow one sperm to contact and fuse with the plasma membrane of the oocyte. If you consider the loss of millions of sperm between entry into the vagina and degradation of the zona pellucida, you can understand why a low sperm count can cause male infertility.

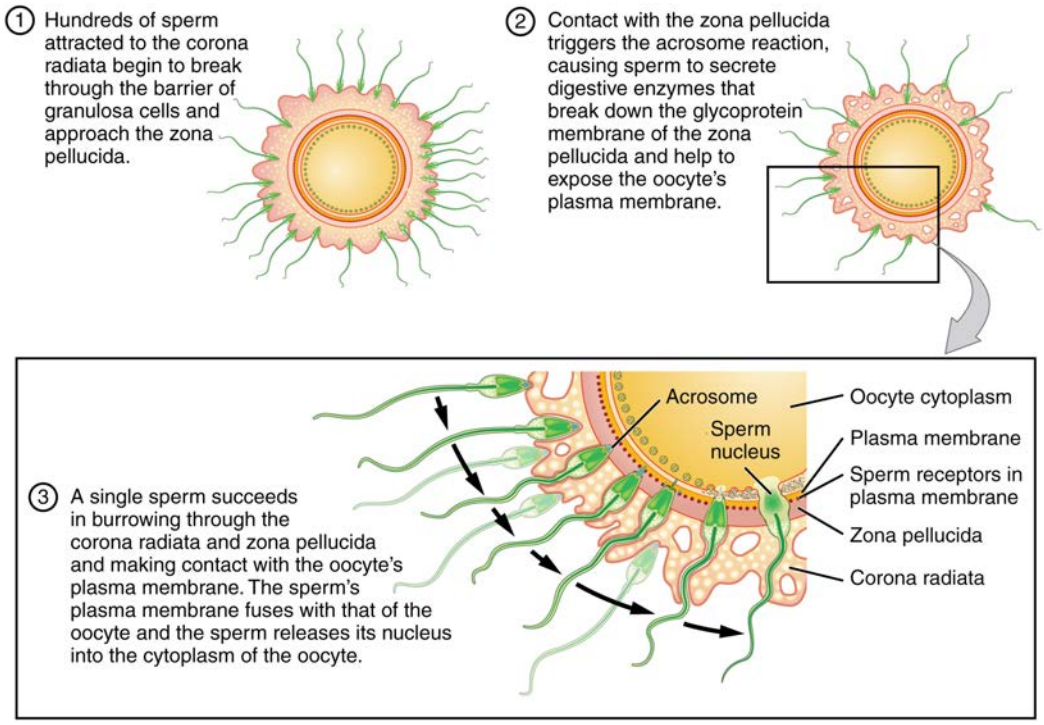



**Figure 28.2 Sperm and the Process of Fertilization** Before fertilization, hundreds of capacitated sperm must break through the surrounding corona radiata and zona pellucida so that one can contact and fuse with the oocyte plasma membrane.

When the first sperm fuses with the oocyte, the oocyte deploys two mechanisms to prevent **polyspermy**, which is penetration by more than one sperm. This is critical because if more than one sperm were to fertilize the oocyte, the resulting zygote would be a triploid organism with three sets of chromosomes. This is incompatible with life.

The first mechanism is the fast block, which involves a near instantaneous change in sodium ion permeability upon binding of the first sperm, depolarizing the oocyte plasma membrane and preventing the fusion of additional sperm cells. The fast block sets in almost immediately and lasts for about a minute, during which time an influx of calcium ions following sperm penetration triggers the second mechanism, the slow block. In this process, referred to as the **cortical reaction**, cortical granules sitting immediately below the oocyte plasma membrane fuse with the membrane and release zonal inhibiting proteins and mucopolysaccharides into the space between the plasma membrane and the zona pellucida. Zonal inhibiting proteins cause the release of any other attached sperm and destroy the oocyte's sperm receptors, thus preventing any more sperm from binding. The mucopolysaccharides then coat the nascent zygote in an impenetrable barrier that, together with hardened zona pellucida, is called a **fertilization membrane**.

## The Zygote

Recall that at the point of fertilization, the oocyte has not yet completed meiosis; all secondary oocytes remain arrested in metaphase of meiosis II until fertilization. Only upon fertilization does the oocyte complete meiosis. The unneeded complement of genetic material that results is stored in a second polar body that is eventually ejected. At this moment, the oocyte has become an ovum, the female haploid gamete. The two haploid nuclei derived from the sperm and oocyte and contained within the egg are referred to as pronuclei. They decondense, expand, and replicate their DNA in preparation for mitosis. The pronuclei then migrate toward each other, their nuclear envelopes disintegrate, and the male- and female-derived genetic material intermingles. This step completes the process of fertilization and results in a single-celled diploid zygote with all the genetic instructions it needs to develop into a human.

Most of the time, a woman releases a single egg during an ovulation cycle. However, in approximately 1 percent of ovulation cycles, two eggs are released and both are fertilized. Two zygotes form, implant, and develop, resulting in the birth of dizygotic (or fraternal) twins. Because dizygotic twins develop from two eggs fertilized by two sperm, they are no more identical than siblings born at different times.

Much less commonly, a zygote can divide into two separate offspring during early development. This results in the birth of monozygotic (or identical) twins. Although the zygote can split as early as the two-cell stage, splitting occurs most commonly during the early blastocyst stage, with roughly 70–100 cells present. These two scenarios are distinct from each other, in that the twin embryos that separated at the two-cell stage will have individual placentas, whereas twin embryos that form from separation at the blastocyst stage will share a placenta and a chorionic cavity.

Everyday CONNECTION

## In Vitro Fertilization

IVF, which stands for in vitro fertilization, is an assisted reproductive technology. In vitro, which in Latin translates to “in glass,” refers to a procedure that takes place outside of the body. There are many different indications for IVF. For example, a woman may produce normal eggs, but the eggs cannot reach the uterus because the uterine tubes are blocked or otherwise compromised. A man may have a low sperm count, low sperm motility, sperm with an unusually high percentage of morphological abnormalities, or sperm that are incapable of penetrating the zona pellucida of an egg.

A typical IVF procedure begins with egg collection. A normal ovulation cycle produces only one oocyte, but the number can be boosted significantly (to 10–20 oocytes) by administering a short course of gonadotropins. The course begins with follicle-stimulating hormone (FSH) analogs, which support the development of multiple follicles, and ends with a luteinizing hormone (LH) analog that triggers ovulation. Right before the ova would be released from the ovary, they are harvested using ultrasound-guided oocyte retrieval. In this procedure, ultrasound allows a physician to visualize mature follicles. The ova are aspirated (sucked out) using a syringe.

In parallel, sperm are obtained from the male partner or from a sperm bank. The sperm are prepared by washing to remove seminal fluid because seminal fluid contains a peptide, FPP (or, fertilization promoting peptide), that—in high concentrations—prevents capacitation of the sperm. The sperm sample is also concentrated, to increase the sperm count per milliliter.

Next, the eggs and sperm are mixed in a petri dish. The ideal ratio is 75,000 sperm to one egg. If there are severe problems with the sperm—for example, the count is exceedingly low, or the sperm are completely nonmotile, or incapable of binding to or penetrating the zona pellucida—a sperm can be injected into an egg. This is called intracytoplasmic sperm injection (ICSI).

The embryos are then incubated until they either reach the eight-cell stage or the blastocyst stage. In the United States, fertilized eggs are typically cultured to the blastocyst stage because this results in a higher pregnancy rate. Finally, the embryos are transferred to a woman’s uterus using a plastic catheter (tube). **Figure 28.3** illustrates the steps involved in IVF.

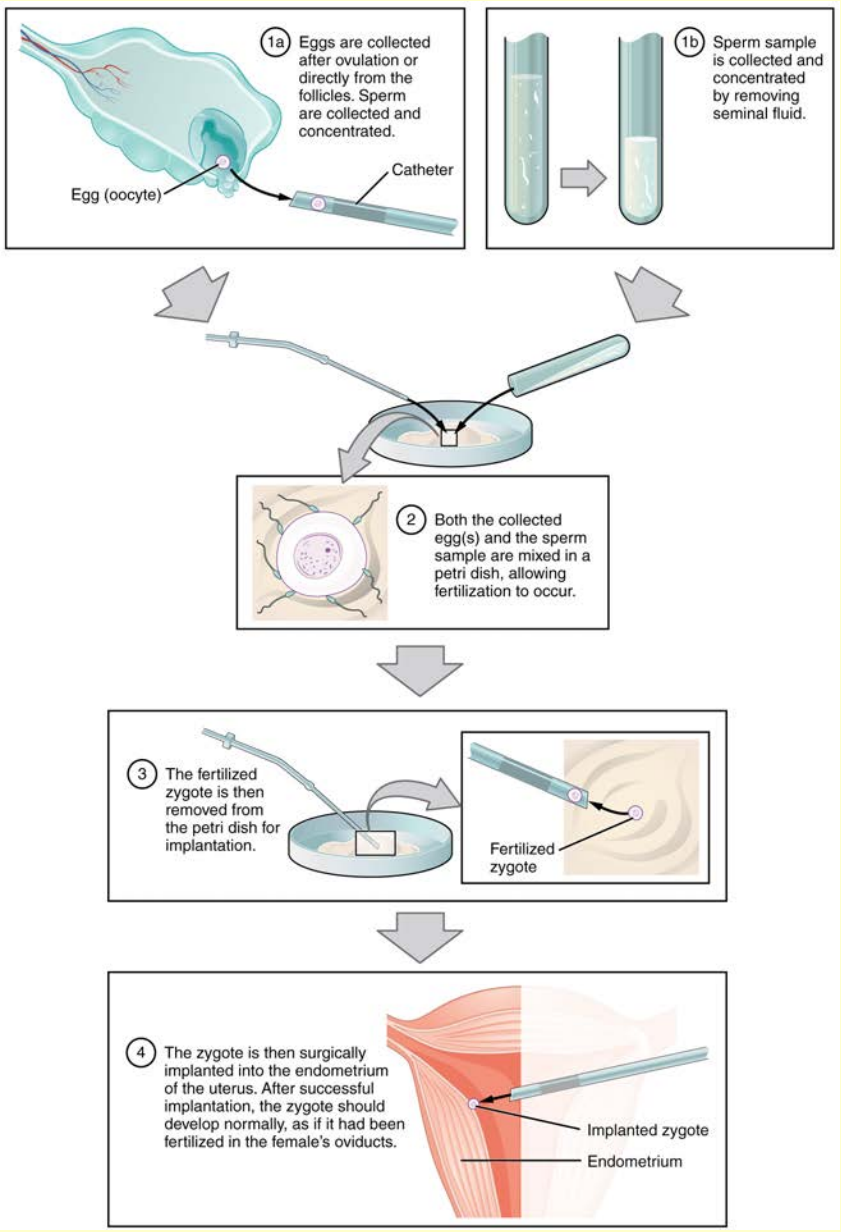



**Figure 28.3 IVF** In vitro fertilization involves egg collection from the ovaries, fertilization in a petri dish, and the transfer of embryos into the uterus.

IVF is a relatively new and still evolving technology, and until recently it was necessary to transfer multiple embryos to achieve a good chance of a pregnancy. Today, however, transferred embryos are much more likely to implant successfully, so countries that regulate the IVF industry cap the number of embryos that can be transferred per cycle at two. This reduces the risk of multiple-birth pregnancies.

The rate of success for IVF is correlated with a woman's age. More than 40 percent of women under 35 succeed in giving birth following IVF, but the rate drops to a little over 10 percent in women over 40.

**Interactive LINK**

Go to this **site (http://openstaxcollege.org/l/fertilization)** to view resources covering various aspects of fertilization, including movies and animations showing sperm structure and motility, ovulation, and fertilization.

# 28.2 | Embryonic Development

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

- Distinguish the stages of embryonic development that occur before implantation
- Describe the process of implantation
- List and describe four embryonic membranes
- Explain gastrulation
- Describe how the placenta is formed and identify its functions
- Explain how an embryo transforms from a flat disc of cells into a three-dimensional shape resembling a human
- Summarize the process of organogenesis

Throughout this chapter, we will express embryonic and fetal ages in terms of weeks from fertilization, commonly called conception. The period of time required for full development of a fetus in utero is referred to as **gestation** (gestare = "to carry" or "to bear"). It can be subdivided into distinct gestational periods. The first 2 weeks of prenatal development are referred to as the pre-embryonic stage. A developing human is referred to as an **embryo** during weeks 3–8, and a **fetus** from the ninth week of gestation until birth. In this section, we'll cover the pre-embryonic and embryonic stages of development, which are characterized by cell division, migration, and differentiation. By the end of the embryonic period, all of the organ systems are structured in rudimentary form, although the organs themselves are either nonfunctional or only semi-functional.

## Pre-implantation Embryonic Development

Following fertilization, the zygote and its associated membranes, together referred to as the **conceptus**, continue to be projected toward the uterus by peristalsis and beating cilia. During its journey to the uterus, the zygote undergoes five or six rapid mitotic cell divisions. Although each **cleavage** results in more cells, it does not increase the total volume of the conceptus (**Figure 28.4**). Each daughter cell produced by cleavage is called a **blastomere** (blastos = "germ," in the sense of a seed or sprout).

Approximately 3 days after fertilization, a 16-cell conceptus reaches the uterus. The cells that had been loosely grouped are now compacted and look more like a solid mass. The name given to this structure is the **morula** (morula = "little mulberry"). Once inside the uterus, the conceptus floats freely for several more days. It continues to divide, creating a ball of approximately 100 cells, and consuming nutritive endometrial secretions called uterine milk while the uterine lining thickens. The ball of now tightly bound cells starts to secrete fluid and organize themselves around a fluid-filled cavity, the **blastocoel**. At this developmental stage, the conceptus is referred to as a **blastocyst**. Within this structure, a group of cells forms into an **inner cell mass**, which is fated to become the embryo. The cells that form the outer shell are called **trophoblasts** (trophe = "to feed" or "to nourish"). These cells will develop into the chorionic sac and the fetal portion of the **placenta** (the organ of nutrient, waste, and gas exchange between mother and the developing offspring).

The inner mass of embryonic cells is totipotent during this stage, meaning that each cell has the potential to differentiate into any cell type in the human body. Totipotency lasts for only a few days before the cells' fates are set as being the precursors to a specific lineage of cells.

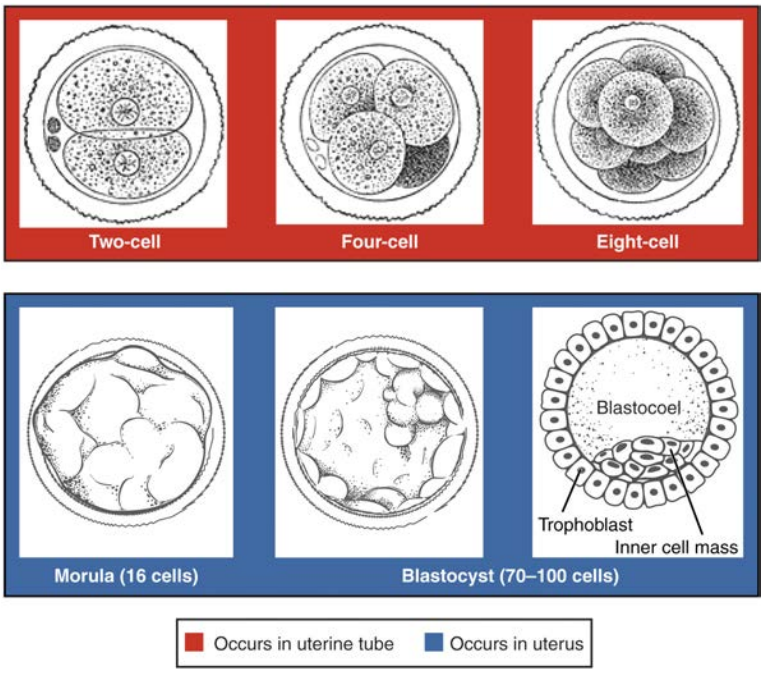



**Figure 28.4 Pre-Embryonic Cleavages** Pre-embryonic cleavages make use of the abundant cytoplasm of the conceptus as the cells rapidly divide without changing the total volume.

As the blastocyst forms, the trophoblast excretes enzymes that begin to degrade the zona pellucida. In a process called "hatching," the conceptus breaks free of the zona pellucida in preparation for implantation.

## Interactive LINK


View this time-lapse **movie (http://openstaxcollege.org/l/conceptus)** of a conceptus starting at day 3. What is the first structure you see? At what point in the movie does the blastocoel first appear? What event occurs at the end of the movie?

## Implantation

At the end of the first week, the blastocyst comes in contact with the uterine wall and adheres to it, embedding itself in the uterine lining via the trophoblast cells. Thus begins the process of **implantation**, which signals the end of the pre-embryonic stage of development (**Figure 28.5**). Implantation can be accompanied by minor bleeding. The blastocyst typically implants in the fundus of the uterus or on the posterior wall. However, if the endometrium is not fully developed and ready to receive the blastocyst, the blastocyst will detach and find a better spot. A significant percentage (50–75 percent) of blastocysts fail to implant; when this occurs, the blastocyst is shed with the endometrium during menses. The high rate of implantation failure is one reason why pregnancy typically requires several ovulation cycles to achieve.

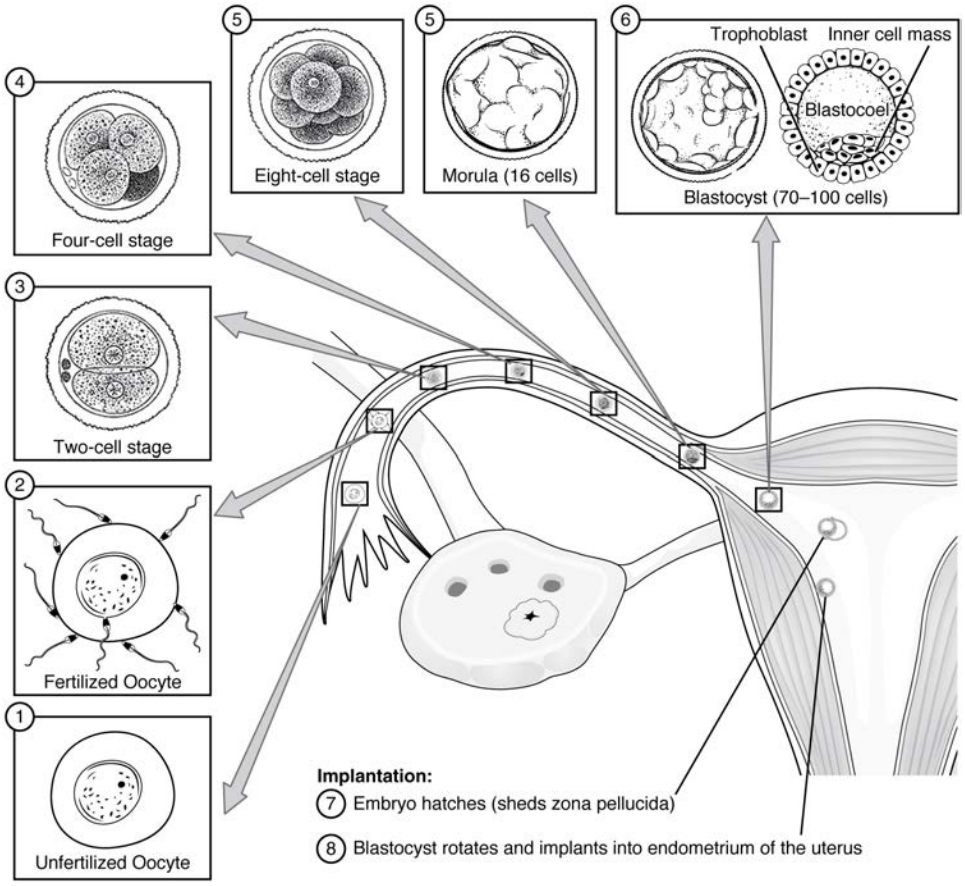



**Figure 28.5 Pre-Embryonic Development** Ovulation, fertilization, pre-embryonic development, and implantation occur at specific locations within the female reproductive system in a time span of approximately 1 week.

When implantation succeeds and the blastocyst adheres to the endometrium, the superficial cells of the trophoblast fuse with each other, forming the **syncytiotrophoblast**, a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall. In response, the uterine mucosa rebuilds itself and envelops the blastocyst (**Figure 28.6**). The trophoblast secretes **human chorionic gonadotropin (hCG)**, a hormone that directs the corpus luteum to survive, enlarge, and continue producing progesterone and estrogen to suppress menses. These functions of hCG are necessary for creating an environment suitable for the developing embryo. As a result of this increased production, hCG accumulates in the maternal bloodstream and is excreted in the urine. Implantation is complete by the middle of the second week. Just a few days after implantation, the trophoblast has secreted enough hCG for an at-home urine pregnancy test to give a positive result.

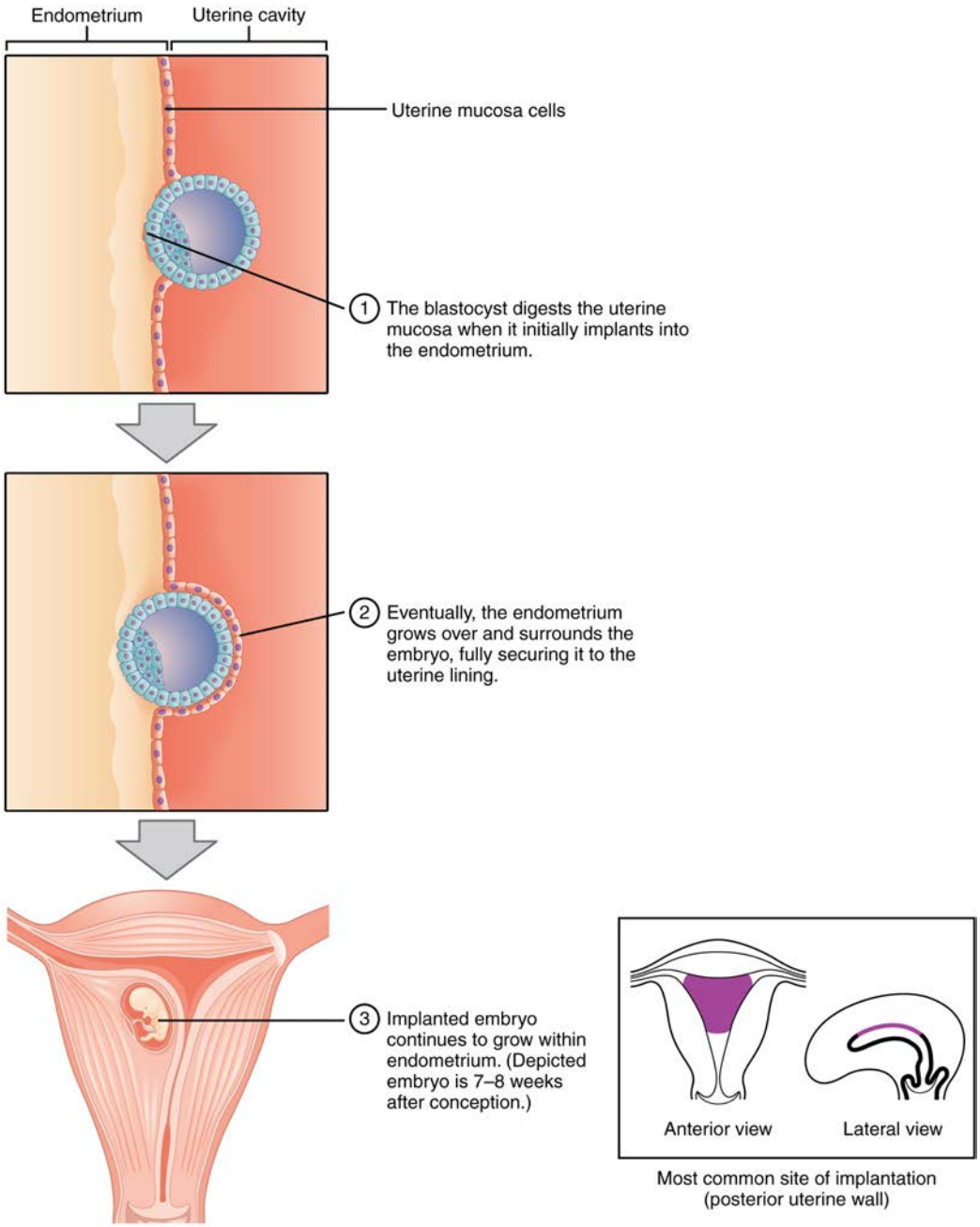



**Figure 28.6 Implantation** During implantation, the trophoblast cells of the blastocyst adhere to the endometrium and digest endometrial cells until it is attached securely.

Most of the time an embryo implants within the body of the uterus in a location that can support growth and development. However, in one to two percent of cases, the embryo implants either outside the uterus (an **ectopic pregnancy**) or in a region of uterus that can create complications for the pregnancy. If the embryo implants in the inferior portion of the uterus, the placenta can potentially grow over the opening of the cervix, a condition call **placenta previa**.

Disorders OF THE...

## Development of the Embryo

In the vast majority of ectopic pregnancies, the embryo does not complete its journey to the uterus and implants in the uterine tube, referred to as a tubal pregnancy. However, there are also ovarian ectopic pregnancies (in which the egg never left the ovary) and abdominal ectopic pregnancies (in which an egg was "lost" to the abdominal cavity during the transfer from ovary to uterine tube, or in which an embryo from a tubal pregnancy re-implanted in the abdomen). Once in the abdominal cavity, an embryo can implant into any well-vascularized structure—the rectouterine cavity (Douglas' pouch), the mesentery of the intestines, and the greater omentum are some common sites.

Tubal pregnancies can be caused by scar tissue within the tube following a sexually transmitted bacterial infection. The scar tissue impedes the progress of the embryo into the uterus—in some cases "snagging" the embryo and, in other cases, blocking the tube completely. Approximately one half of tubal pregnancies resolve spontaneously. Implantation in a uterine tube causes bleeding, which appears to stimulate smooth muscle contractions and expulsion of the embryo. In the remaining cases, medical or surgical intervention is necessary. If an ectopic pregnancy is detected early, the embryo's development can be arrested by the administration of the cytotoxic drug methotrexate, which inhibits the metabolism of folic acid. If diagnosis is late and the uterine tube is already ruptured, surgical repair is essential.

Even if the embryo has successfully found its way to the uterus, it does not always implant in an optimal location (the fundus or the posterior wall of the uterus). Placenta previa can result if an embryo implants close to the internal os of the uterus (the internal opening of the cervix). As the fetus grows, the placenta can partially or completely cover the opening of the cervix (**Figure 28.7**). Although it occurs in only 0.5 percent of pregnancies, placenta previa is the leading cause of antepartum hemorrhage (profuse vaginal bleeding after week 24 of pregnancy but prior to childbirth).

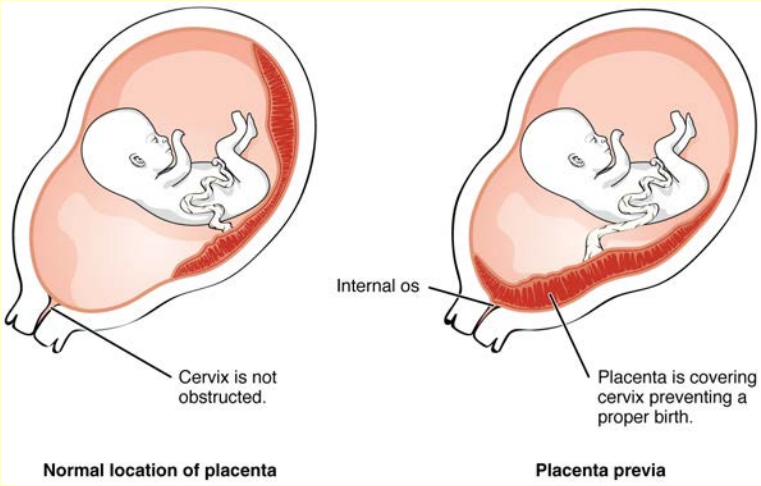



**Figure 28.7 Placenta Previa** An embryo that implants too close to the opening of the cervix can lead to placenta previa, a condition in which the placenta partially or completely covers the cervix.

## Embryonic Membranes

During the second week of development, with the embryo implanted in the uterus, cells within the blastocyst start to organize into layers. Some grow to form the extra-embryonic membranes needed to support and protect the growing embryo: the amnion, the yolk sac, the allantois, and the chorion.

At the beginning of the second week, the cells of the inner cell mass form into a two-layered disc of embryonic cells, and a space—the **amniotic cavity**—opens up between it and the trophoblast (**Figure 28.8**). Cells from the upper layer of the disc (the **epiblast**) extend around the amniotic cavity, creating a membranous sac that forms into the **amnion** by the end of the second week. The amnion fills with amniotic fluid and eventually grows to surround the embryo. Early in development, amniotic fluid consists almost entirely of a filtrate of maternal plasma, but as the kidneys of the fetus begin to function at approximately the eighth week, they add urine to the volume of amniotic fluid. Floating within the amniotic fluid, the embryo—and later, the fetus—is protected from trauma and rapid temperature changes. It can move freely within the fluid and can prepare for swallowing and breathing out of the uterus.

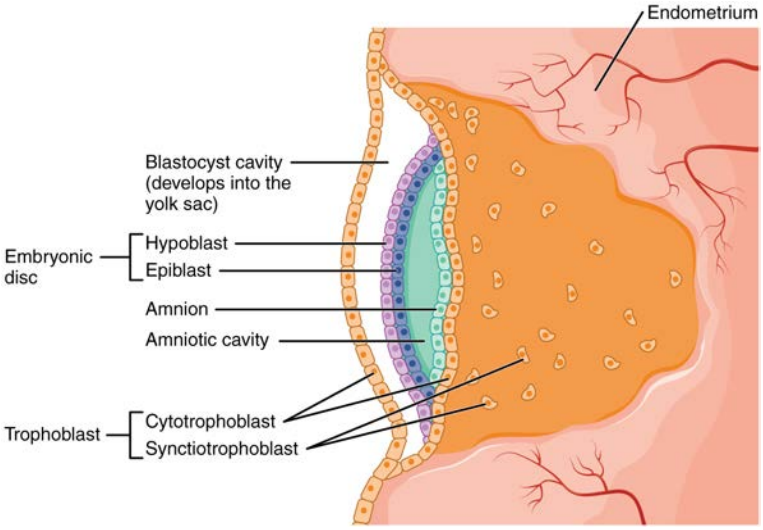



**Figure 28.8 Development of the Embryonic Disc** Formation of the embryonic disc leaves spaces on either side that develop into the amniotic cavity and the yolk sac.

On the ventral side of the embryonic disc, opposite the amnion, cells in the lower layer of the embryonic disk (the **hypoblast**) extend into the blastocyst cavity and form a **yolk sac**. The yolk sac supplies some nutrients absorbed from the trophoblast and also provides primitive blood circulation to the developing embryo for the second and third week of development. When the placenta takes over nourishing the embryo at approximately week 4, the yolk sac has been greatly reduced in size and its main function is to serve as the source of blood cells and germ cells (cells that will give rise to gametes). During week 3, a finger-like outpocketing of the yolk sac develops into the **allantois**, a primitive excretory duct of the embryo that will become part of the urinary bladder. Together, the stalks of the yolk sac and allantois establish the outer structure of the umbilical cord.

The last of the extra-embryonic membranes is the **chorion**, which is the one membrane that surrounds all others. The development of the chorion will be discussed in more detail shortly, as it relates to the growth and development of the placenta.

## Embryogenesis

As the third week of development begins, the two-layered disc of cells becomes a three-layered disc through the process of **gastrulation**, during which the cells transition from totipotency to multipotency. The embryo, which takes the shape of an oval-shaped disc, forms an indentation called the **primitive streak** along the dorsal surface of the epiblast. A node at the caudal or “tail” end of the primitive streak emits growth factors that direct cells to multiply and migrate. Cells migrate toward and through the primitive streak and then move laterally to create two new layers of cells. The first layer is the **endoderm**, a sheet of cells that displaces the hypoblast and lies adjacent to the yolk sac. The second layer of cells fills in as the middle layer, or **mesoderm**. The cells of the epiblast that remain (not having migrated through the primitive streak) become the **ectoderm** (Figure 28.9).

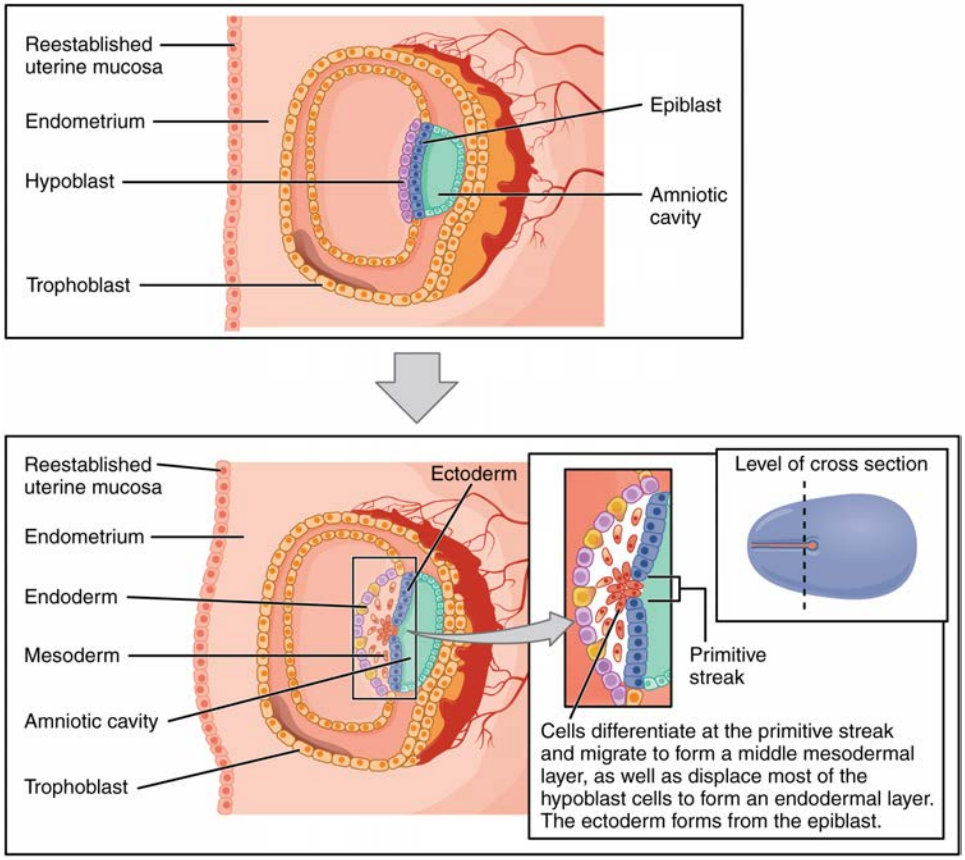



**Figure 28.9 Germ Layers** Formation of the three primary germ layers occurs during the first 2 weeks of development. The embryo at this stage is only a few millimeters in length.

Each of these germ layers will develop into specific structures in the embryo. Whereas the ectoderm and endoderm form tightly connected epithelial sheets, the mesodermal cells are less organized and exist as a loosely connected cell community. The ectoderm gives rise to cell lineages that differentiate to become the central and peripheral nervous systems, sensory organs, epidermis, hair, and nails. Mesodermal cells ultimately become the skeleton, muscles, connective tissue, heart, blood vessels, and kidneys. The endoderm goes on to form the epithelial lining of the gastrointestinal tract, liver, and pancreas, as well as the lungs (**Figure 28.10**).

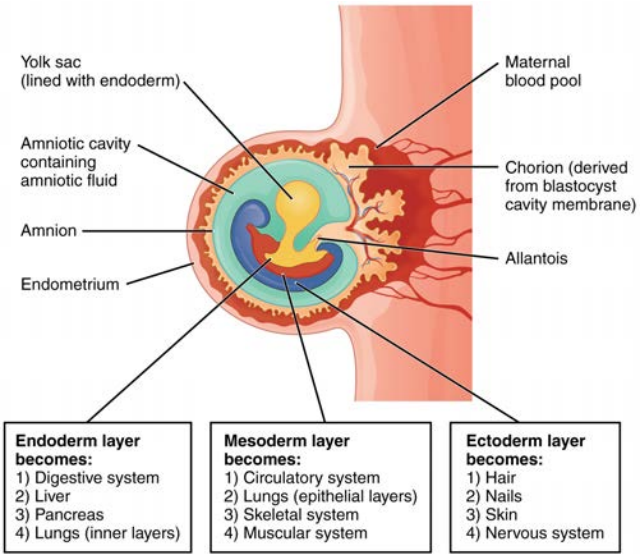



**Figure 28.10 Fates of Germ Layers in Embryo** Following gastrulation of the embryo in the third week, embryonic cells of the ectoderm, mesoderm, and endoderm begin to migrate and differentiate into the cell lineages that will give rise to mature organs and organ systems in the infant.

## Development of the Placenta

During the first several weeks of development, the cells of the endometrium—referred to as decidual cells—nourish the nascent embryo. During prenatal weeks 4–12, the developing placenta gradually takes over the role of feeding the embryo, and the decidual cells are no longer needed. The mature placenta is composed of tissues derived from the embryo, as well as maternal tissues of the endometrium. The placenta connects to the conceptus via the **umbilical cord**, which carries deoxygenated blood and wastes from the fetus through two umbilical arteries; nutrients and oxygen are carried from the mother to the fetus through the single umbilical vein. The umbilical cord is surrounded by the amnion, and the spaces within the cord around the blood vessels are filled with Wharton's jelly, a mucous connective tissue.

The maternal portion of the placenta develops from the deepest layer of the endometrium, the decidua basalis. To form the embryonic portion of the placenta, the syncytiotrophoblast and the underlying cells of the trophoblast (cytotrophoblast cells) begin to proliferate along with a layer of extraembryonic mesoderm cells. These form the **chorionic membrane**, which envelops the entire conceptus as the chorion. The chorionic membrane forms finger-like structures called **chorionic villi** that burrow into the endometrium like tree roots, making up the fetal portion of the placenta. The cytotrophoblast cells perforate the chorionic villi, burrow farther into the endometrium, and remodel maternal blood vessels to augment maternal blood flow surrounding the villi. Meanwhile, fetal mesenchymal cells derived from the mesoderm fill the villi and differentiate into blood vessels, including the three umbilical blood vessels that connect the embryo to the developing placenta (**Figure 28.11**).

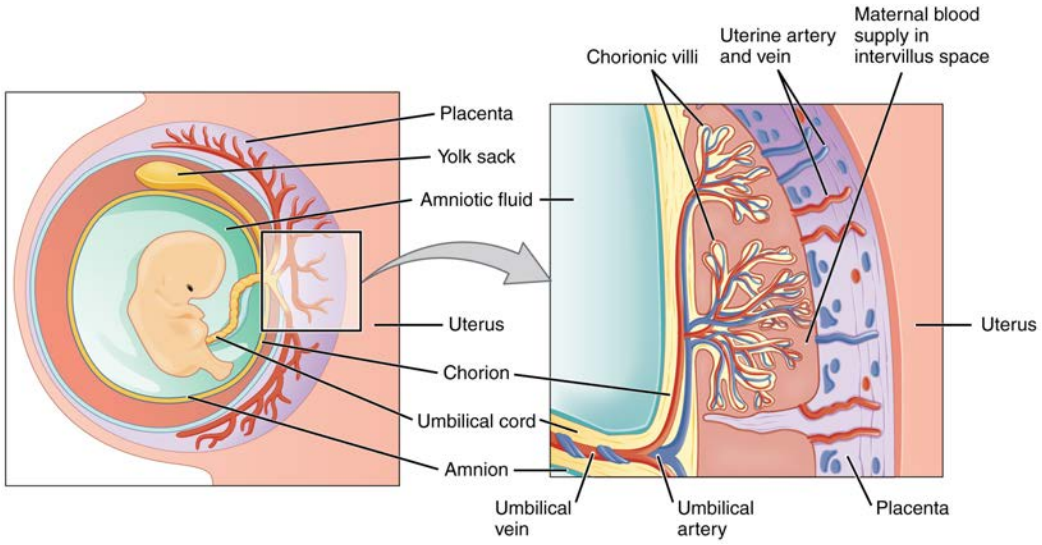



**Figure 28.11 Cross-Section of the Placenta** In the placenta, maternal and fetal blood components are conducted through the surface of the chorionic villi, but maternal and fetal bloodstreams never mix directly.

The placenta develops throughout the embryonic period and during the first several weeks of the fetal period; **placentation** is complete by weeks 14–16. As a fully developed organ, the placenta provides nutrition and excretion, respiration, and endocrine function (**Table 28.1** and **Figure 28.12**). It receives blood from the fetus through the umbilical arteries. Capillaries in the chorionic villi filter fetal wastes out of the blood and return clean, oxygenated blood to the fetus through the umbilical vein. Nutrients and oxygen are transferred from maternal blood surrounding the villi through the capillaries and into the fetal bloodstream. Some substances move across the placenta by simple diffusion. Oxygen, carbon dioxide, and any other lipid-soluble substances take this route. Other substances move across by facilitated diffusion. This includes water-soluble glucose. The fetus has a high demand for amino acids and iron, and those substances are moved across the placenta by active transport.

Maternal and fetal blood does not commingle because blood cells cannot move across the placenta. This separation prevents the mother's cytotoxic T cells from reaching and subsequently destroying the fetus, which bears "non-self" antigens. Further, it ensures the fetal red blood cells do not enter the mother's circulation and trigger antibody development (if they carry "non-self" antigens)—at least until the final stages of pregnancy or birth. This is the reason that, even in the absence of preventive treatment, an $Rh^-$ mother doesn't develop antibodies that could cause hemolytic disease in her first $Rh^+$ fetus.

Although blood cells are not exchanged, the chorionic villi provide ample surface area for the two-way exchange of substances between maternal and fetal blood. The rate of exchange increases throughout gestation as the villi become thinner and increasingly branched. The placenta is permeable to lipid-soluble fetotoxic substances: alcohol, nicotine, barbiturates, antibiotics, certain pathogens, and many other substances that can be dangerous or fatal to the developing embryo or fetus. For these reasons, pregnant women should avoid fetotoxic substances. Alcohol consumption by pregnant women, for example, can result in a range of abnormalities referred to as fetal alcohol spectrum disorders (FASD). These include organ and facial malformations, as well as cognitive and behavioral disorders.

**Functions of the Placenta**

| Nutrition and digestion | Respiration | Endocrine function |
|---|---|---|
| Mediates diffusion of maternal glucose, amino acids, fatty acids, vitamins, and minerals<br>Stores nutrients during early pregnancy to accommodate increased fetal demand later in pregnancy<br>Excretes and filters fetal nitrogenous wastes into maternal blood | Mediates maternal-to-fetal oxygen transport and fetal-to-maternal carbon dioxide transport | Secretes several hormones, including hCG, estrogens, and progesterone, to maintain the pregnancy and stimulate maternal and fetal development<br>Mediates the transmission of maternal hormones into fetal blood and vice versa |

**Table 28.1**

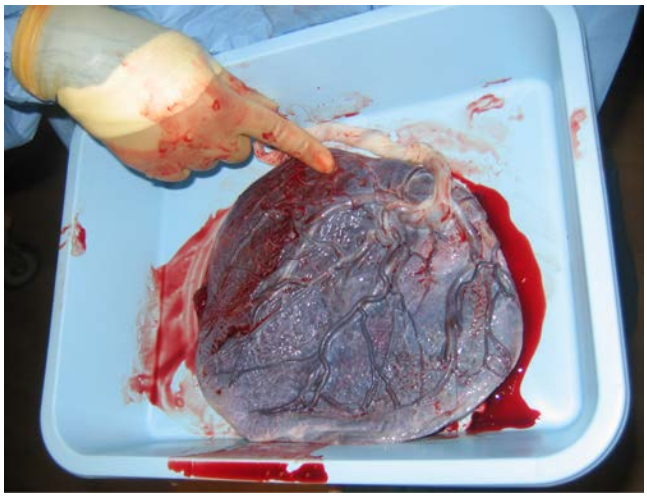


**Figure 28.12 Placenta** This post-expulsion placenta and umbilical cord (white) are viewed from the fetal side.

## Organogenesis

Following gastrulation, rudiments of the central nervous system develop from the ectoderm in the process of **neurulation** (**Figure 28.13**). Specialized neuroectodermal tissues along the length of the embryo thicken into the **neural plate**. During the fourth week, tissues on either side of the plate fold upward into a **neural fold**. The two folds converge to form the **neural tube**. The tube lies atop a rod-shaped, mesoderm-derived **notochord**, which eventually becomes the nucleus pulposus of intervertebral discs. Block-like structures called **somites** form on either side of the tube, eventually differentiating into the axial skeleton, skeletal muscle, and dermis. During the fourth and fifth weeks, the anterior neural tube dilates and subdivides to form vesicles that will become the brain structures.

Folate, one of the B vitamins, is important to the healthy development of the neural tube. A deficiency of maternal folate in the first weeks of pregnancy can result in neural tube defects, including spina bifida—a birth defect in which spinal tissue protrudes through the newborn's vertebral column, which has failed to completely close. A more severe neural tube defect is anencephaly, a partial or complete absence of brain tissue.

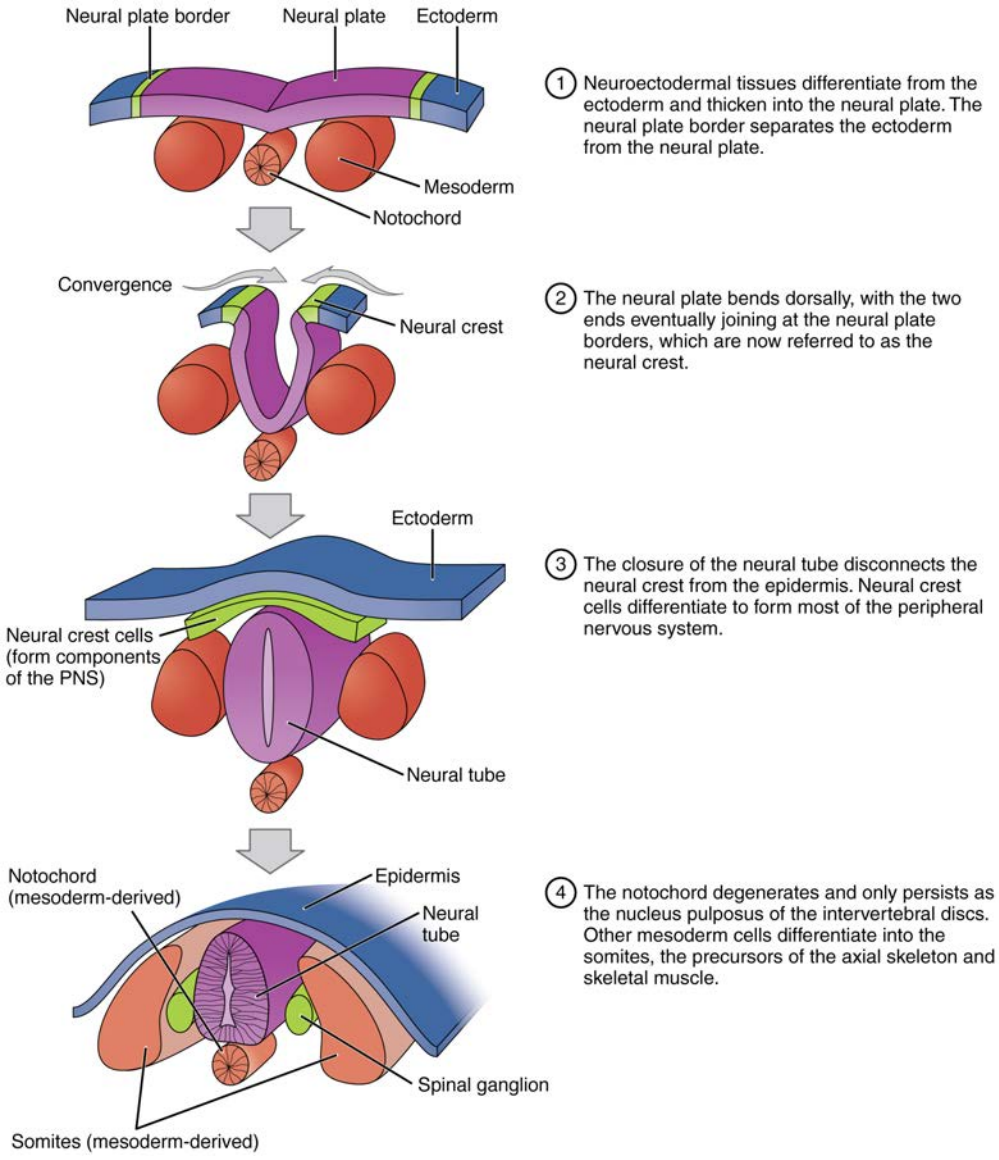



**Figure 28.13 Neurulation** The embryonic process of neurulation establishes the rudiments of the future central nervous system and skeleton.

The embryo, which begins as a flat sheet of cells, begins to acquire a cylindrical shape through the process of **embryonic folding** (Figure 28.14). The embryo folds laterally and again at either end, forming a C-shape with distinct head and tail ends. The embryo envelops a portion of the yolk sac, which protrudes with the umbilical cord from what will become the abdomen. The folding essentially creates a tube, called the primitive gut, that is lined by the endoderm. The amniotic sac, which was sitting on top of the flat embryo, envelops the embryo as it folds.

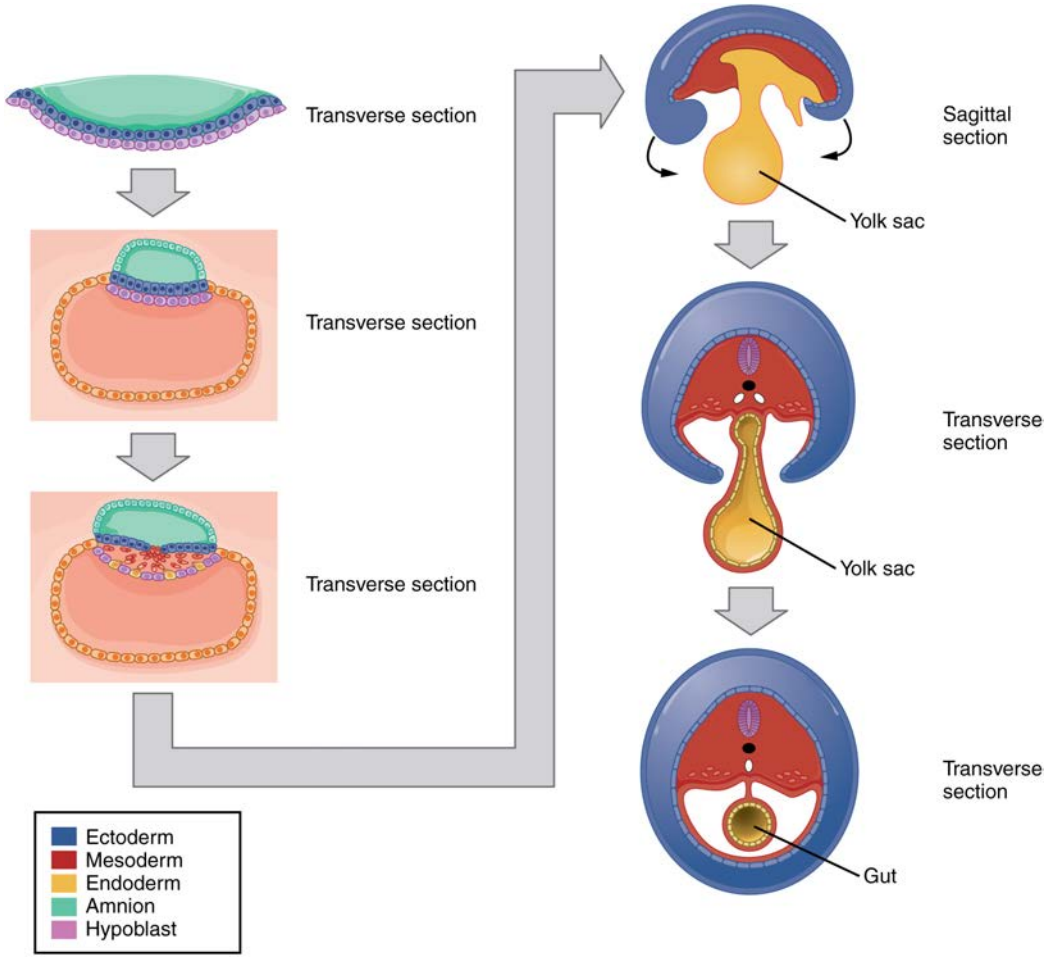



**Figure 28.14 Embryonic Folding** Embryonic folding converts a flat sheet of cells into a hollow, tube-like structure.

Within the first 8 weeks of gestation, a developing embryo establishes the rudimentary structures of all of its organs and tissues from the ectoderm, mesoderm, and endoderm. This process is called **organogenesis**.

Like the central nervous system, the heart also begins its development in the embryo as a tube-like structure, connected via capillaries to the chorionic villi. Cells of the primitive tube-shaped heart are capable of electrical conduction and contraction. The heart begins beating in the beginning of the fourth week, although it does not actually pump embryonic blood until a week later, when the oversized liver has begun producing red blood cells. (This is a temporary responsibility of the embryonic liver that the bone marrow will assume during fetal development.) During weeks 4–5, the eye pits form, limb buds become apparent, and the rudiments of the pulmonary system are formed.

During the sixth week, uncontrolled fetal limb movements begin to occur. The gastrointestinal system develops too rapidly for the embryonic abdomen to accommodate it, and the intestines temporarily loop into the umbilical cord. Paddle-shaped hands and feet develop fingers and toes by the process of apoptosis (programmed cell death), which causes the tissues between the fingers to disintegrate. By week 7, the facial structure is more complex and includes nostrils, outer ears, and lenses (**Figure 28.15**). By the eighth week, the head is nearly as large as the rest of the embryo's body, and all major brain structures are in place. The external genitalia are apparent, but at this point, male and female embryos are indistinguishable. Bone begins to replace cartilage in the embryonic skeleton through the process of ossification. By the end of the embryonic period, the embryo is approximately 3 cm (1.2 in) from crown to rump and weighs approximately 8 g (0.25 oz).

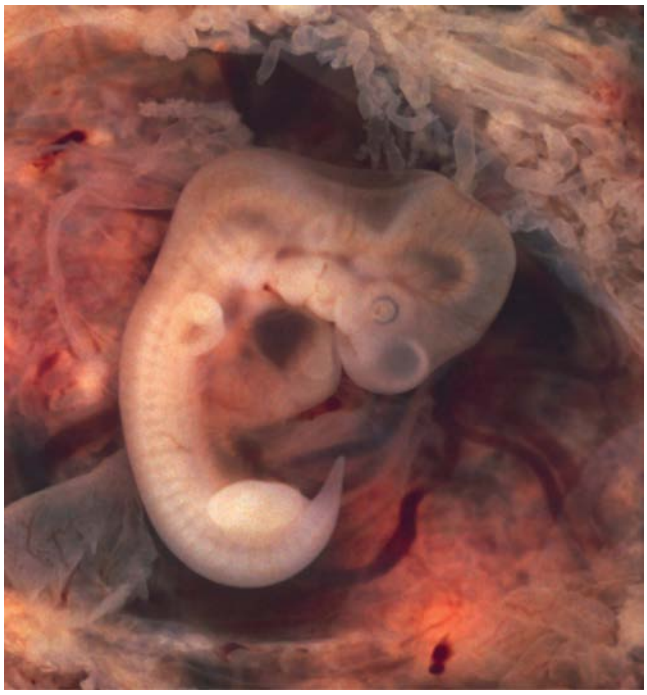


**Figure 28.15 Embryo at 7 Weeks** An embryo at the end of 7 weeks of development is only 10 mm in length, but its developing eyes, limb buds, and tail are already visible. (This embryo was derived from an ectopic pregnancy.) (credit: Ed Uthman)

Interactive LINK

Use this interactive **tool (http://openstaxcollege.org/l/embryogenesis)** to view the process of embryogenesis from the perspective of the conceptus (left panel), as well as fetal development viewed from a maternal cross-section (right panel). Can you identify when neurulation occurs in the embryo?

## 28.3 | Fetal Development

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

- Differentiate between the embryonic period and the fetal period
- Briefly describe the process of sexual differentiation
- Describe the fetal circulatory system and explain the role of the shunts
- Trace the development of a fetus from the end of the embryonic period to birth

As you will recall, a developing human is called a fetus from the ninth week of gestation until birth. This 30-week period of development is marked by continued cell growth and differentiation, which fully develop the structures and functions of the immature organ systems formed during the embryonic period. The completion of fetal development results in a newborn who, although still immature in many ways, is capable of survival outside the womb.

## Sexual Differentiation

Sexual differentiation does not begin until the fetal period, during weeks 9–12. Embryonic males and females, though genetically distinguishable, are morphologically identical (**Figure 28.16**). Bipotential gonads, or gonads that can develop into male or female sexual organs, are connected to a central cavity called the cloaca via Müllerian ducts and Wolffian ducts. (The cloaca is an extension of the primitive gut.) Several events lead to sexual differentiation during this period.

During male fetal development, the bipotential gonads become the testes and associated epididymis. The Müllerian ducts degenerate. The Wolffian ducts become the vas deferens, and the cloaca becomes the urethra and rectum.

During female fetal development, the bipotential gonads develop into ovaries. The Wolffian ducts degenerate. The Müllerian ducts become the uterine tubes and uterus, and the cloaca divides and develops into a vagina, a urethra, and a rectum.

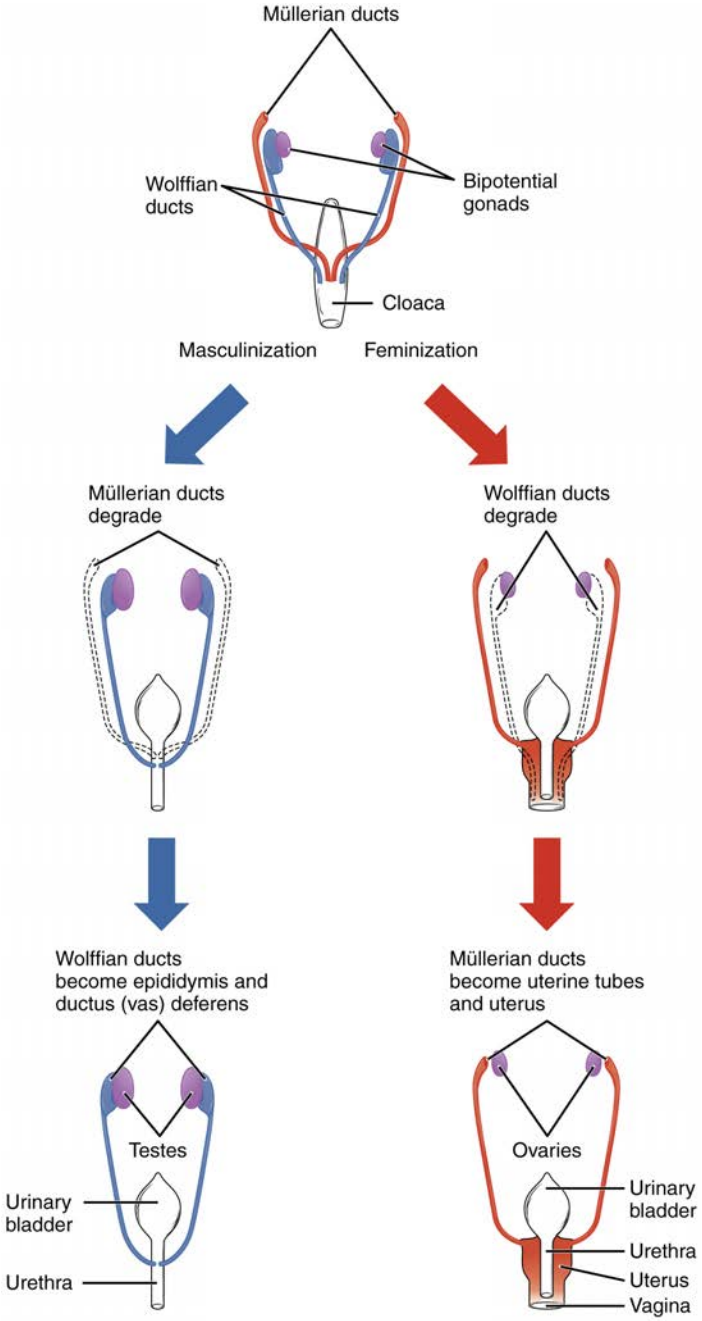



**Figure 28.16 Sexual Differentiation** Differentiation of the male and female reproductive systems does not occur until the fetal period of development.

## The Fetal Circulatory System

During prenatal development, the fetal circulatory system is integrated with the placenta via the umbilical cord so that the fetus receives both oxygen and nutrients from the placenta. However, after childbirth, the umbilical cord is severed, and the newborn's circulatory system must be reconfigured. When the heart first forms in the embryo, it exists as two parallel tubes derived from mesoderm and lined with endothelium, which then fuse together. As the embryo develops into a fetus, the tube-shaped heart folds and further differentiates into the four chambers present in a mature heart. Unlike a mature cardiovascular system, however, the fetal cardiovascular system also includes circulatory shortcuts, or shunts. A **shunt** is an anatomical (or sometimes surgical) diversion that allows blood flow to bypass immature organs such as the lungs and liver until childbirth.

The placenta provides the fetus with necessary oxygen and nutrients via the umbilical vein. (Remember that veins carry blood toward the heart. In this case, the blood flowing to the fetal heart is oxygenated because it comes from the placenta. The respiratory system is immature and cannot yet oxygenate blood on its own.) From the umbilical vein, the oxygenated blood flows toward the inferior vena cava, all but bypassing the immature liver, via the **ductus venosus** shunt (**Figure 28.17**). The liver receives just a trickle of blood, which is all that it needs in its immature, semifunctional state. Blood flows from the inferior vena cava to the right atrium, mixing with fetal venous blood along the way.

Although the fetal liver is semifunctional, the fetal lungs are nonfunctional. The fetal circulation therefore bypasses the lungs by shifting some of the blood through the **foramen ovale**, a shunt that directly connects the right and left atria and avoids the pulmonary trunk altogether. Most of the rest of the blood is pumped to the right ventricle, and from there, into the pulmonary trunk, which splits into pulmonary arteries. However, a shunt within the pulmonary artery, the **ductus arteriosus**, diverts a portion of this blood into the aorta. This ensures that only a small volume of oxygenated blood passes through the immature pulmonary circuit, which has only minor metabolic requirements. Blood vessels of uninflated lungs have high resistance to flow, a condition that encourages blood to flow to the aorta, which presents much lower resistance. The oxygenated blood moves through the foramen ovale into the left atrium, where it mixes with the now deoxygenated blood returning from the pulmonary circuit. This blood then moves into the left ventricle, where it is pumped into the aorta. Some of this blood moves through the coronary arteries into the myocardium, and some moves through the carotid arteries to the brain.

The descending aorta carries partially oxygenated and partially deoxygenated blood into the lower regions of the body. It eventually passes into the umbilical arteries through branches of the internal iliac arteries. The deoxygenated blood collects waste as it circulates through the fetal body and returns to the umbilical cord. Thus, the two umbilical arteries carry blood low in oxygen and high in carbon dioxide and fetal wastes. This blood is filtered through the placenta, where wastes diffuse into the maternal circulation. Oxygen and nutrients from the mother diffuse into the placenta and from there into the fetal blood, and the process repeats.

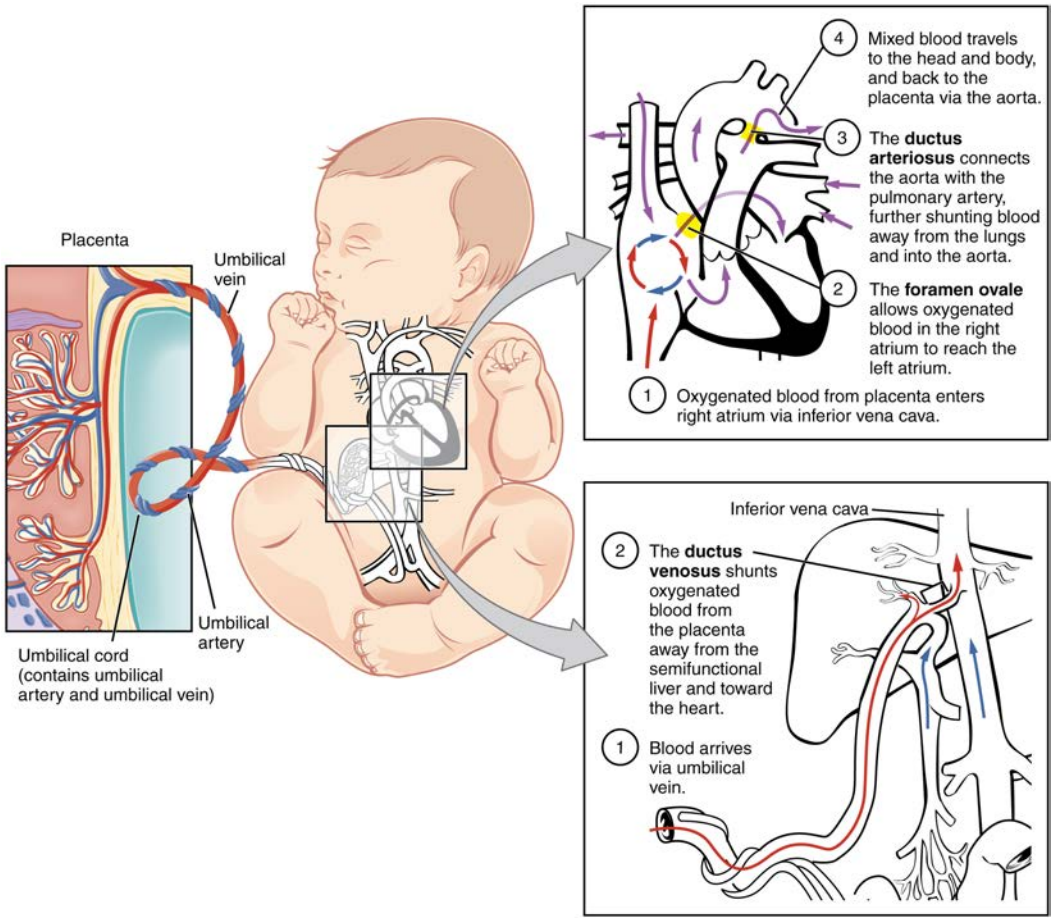



**Figure 28.17 Fetal Circulatory System** The fetal circulatory system includes three shunts to divert blood from undeveloped and partially functioning organs, as well as blood supply to and from the placenta.

## Other Organ Systems

During weeks 9–12 of fetal development, the brain continues to expand, the body elongates, and ossification continues. Fetal movements are frequent during this period, but are jerky and not well-controlled. The bone marrow begins to take over the process of erythrocyte production—a task that the liver performed during the embryonic period. The liver now secretes bile. The fetus circulates amniotic fluid by swallowing it and producing urine. The eyes are well-developed by this stage, but the eyelids are fused shut. The fingers and toes begin to develop nails. By the end of week 12, the fetus measures approximately 9 cm (3.5 in) from crown to rump.

Weeks 13–16 are marked by sensory organ development. The eyes move closer together; blinking motions begin, although the eyes remain sealed shut. The lips exhibit sucking motions. The ears move upward and lie flatter against the head. The scalp begins to grow hair. The excretory system is also developing: the kidneys are well-formed, and **meconium**, or fetal feces, begins to accumulate in the intestines. Meconium consists of ingested amniotic fluid, cellular debris, mucus, and bile.

During approximately weeks 16–20, as the fetus grows and limb movements become more powerful, the mother may begin to feel **quickening**, or fetal movements. However, space restrictions limit these movements and typically force the growing fetus into the "fetal position," with the arms crossed and the legs bent at the knees. Sebaceous glands coat the skin with a waxy, protective substance called **vernix caseosa** that protects and moisturizes the skin and may provide lubrication during childbirth. A silky hair called **lanugo** also covers the skin during weeks 17–20, but it is shed as the fetus continues to grow. Extremely premature infants sometimes exhibit residual lanugo.

Developmental weeks 21–30 are characterized by rapid weight gain, which is important for maintaining a stable body temperature after birth. The bone marrow completely takes over erythrocyte synthesis, and the axons of the spinal cord begin to be myelinated, or coated in the electrically insulating glial cell sheaths that are necessary for efficient nervous system functioning. (The process of myelination is not completed until adolescence.) During this period, the fetus grows eyelashes. The eyelids are no longer fused and can be opened and closed. The lungs begin producing surfactant, a substance that reduces surface tension in the lungs and assists proper lung expansion after birth. Inadequate surfactant production in premature newborns may result in respiratory distress syndrome, and as a result, the newborn may require surfactant replacement therapy, supplemental oxygen, or maintenance in a continuous positive airway pressure (CPAP) chamber during their first days or weeks of life. In male fetuses, the testes descend into the scrotum near the end of this period. The

fetus at 30 weeks measures 28 cm (11 in) from crown to rump and exhibits the approximate body proportions of a full-term newborn, but still is much leaner.

## Interactive LINK

Visit this **site (http://openstaxcollege.org/l/pregstages)** for a summary of the stages of pregnancy, as experienced by the mother, and view the stages of development of the fetus throughout gestation. At what point in fetal development can a regular heartbeat be detected?

The fetus continues to lay down subcutaneous fat from week 31 until birth. The added fat fills out the hypodermis, and the skin transitions from red and wrinkled to soft and pink. Lanugo is shed, and the nails grow to the tips of the fingers and toes. Immediately before birth, the average crown-to-rump length is 35.5–40.5 cm (14–16 in), and the fetus weighs approximately 2.5–4 kg (5.5–8.8 lbs). Once born, the newborn is no longer confined to the fetal position, so subsequent measurements are made from head-to-toe instead of from crown-to-rump. At birth, the average length is approximately 51 cm (20 in).

## Disorders OF THE...

### Developing Fetus

Throughout the second half of gestation, the fetal intestines accumulate a tarry, greenish black meconium. The newborn's first stools consist almost entirely of meconium; they later transition to seedy yellow stools or slightly formed tan stools as meconium is cleared and replaced with digested breast milk or formula, respectively. Unlike these later stools, meconium is sterile; it is devoid of bacteria because the fetus is in a sterile environment and has not consumed any breast milk or formula. Typically, an infant does not pass meconium until after birth. However, in 5–20 percent of births, the fetus has a bowel movement in utero, which can cause major complications in the newborn.

The passage of meconium in the uterus signals fetal distress, particularly fetal hypoxia (i.e., oxygen deprivation). This may be caused by maternal drug abuse (especially tobacco or cocaine), maternal hypertension, depletion of amniotic fluid, long labor or difficult birth, or a defect in the placenta that prevents it from delivering adequate oxygen to the fetus. Meconium passage is typically a complication of full-term or post-term newborns because it is rarely passed before 34 weeks of gestation, when the gastrointestinal system has matured and is appropriately controlled by nervous system stimuli. Fetal distress can stimulate the vagus nerve to trigger gastrointestinal peristalsis and relaxation of the anal sphincter. Notably, fetal hypoxic stress also induces a gasping reflex, increasing the likelihood that meconium will be inhaled into the fetal lungs.

Although meconium is a sterile substance, it interferes with the antibiotic properties of the amniotic fluid and makes the newborn and mother more vulnerable to bacterial infections at birth and during the perinatal period. Specifically, inflammation of the fetal membranes, inflammation of the uterine lining, or neonatal sepsis (infection in the newborn) may occur. Meconium also irritates delicate fetal skin and can cause a rash.

The first sign that a fetus has passed meconium usually does not come until childbirth, when the amniotic sac ruptures. Normal amniotic fluid is clear and watery, but amniotic fluid in which meconium has been passed is stained greenish or yellowish. Antibiotics given to the mother may reduce the incidence of maternal bacterial infections, but it is critical that meconium is aspirated from the newborn before the first breath. Under these conditions, an obstetrician will extensively aspirate the infant's airways as soon as the head is delivered, while the rest of the infant's body is still inside the birth canal.

Aspiration of meconium with the first breath can result in labored breathing, a barrel-shaped chest, or a low Apgar score. An obstetrician can identify meconium aspiration by listening to the lungs with a stethoscope for a coarse rattling sound. Blood gas tests and chest X-rays of the infant can confirm meconium aspiration. Inhaled meconium after birth could obstruct a newborn's airways leading to alveolar collapse, interfere with surfactant function by stripping it from the lungs, or cause pulmonary inflammation or hypertension. Any of these complications will make the newborn much more vulnerable to pulmonary infection, including pneumonia.

## 28.4 | Maternal Changes During Pregnancy, Labor, and Birth

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

- Explain how estrogen, progesterone, and hCG are involved in maintaining pregnancy
- List the contributors to weight gain during pregnancy
- Describe the major changes to the maternal digestive, circulatory, and integumentary systems during pregnancy
- Summarize the events leading to labor
- Identify and describe each of the three stages of childbirth

A full-term pregnancy lasts approximately 270 days (approximately 38.5 weeks) from conception to birth. Because it is easier to remember the first day of the last menstrual period (LMP) than to estimate the date of conception, obstetricians set the due date as 284 days (approximately 40.5 weeks) from the LMP. This assumes that conception occurred on day 14 of the woman's cycle, which is usually a good approximation. The 40 weeks of an average pregnancy are usually discussed in terms of three **trimesters**, each approximately 13 weeks. During the second and third trimesters, the pre-pregnancy uterus—about the size of a fist—grows dramatically to contain the fetus, causing a number of anatomical changes in the mother (**Figure 28.18**).

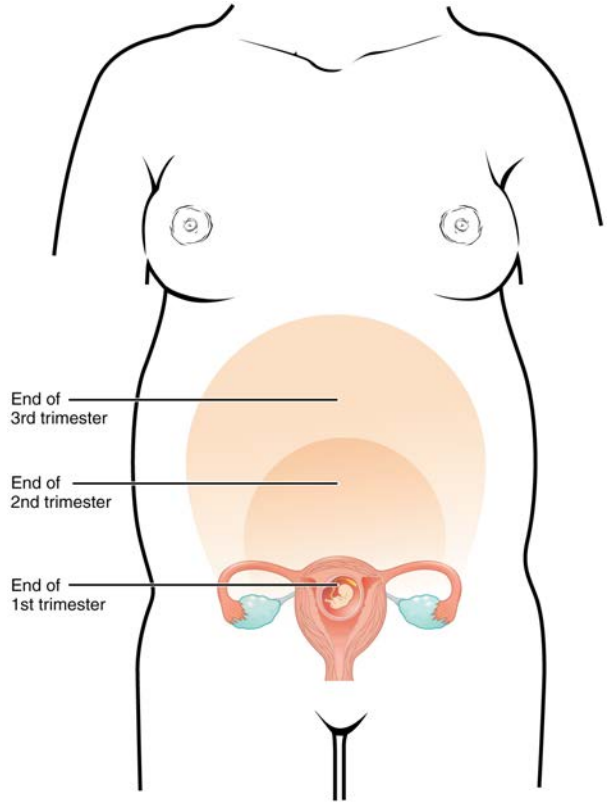



**Figure 28.18 Size of Uterus throughout Pregnancy** The uterus grows throughout pregnancy to accommodate the fetus.

## Effects of Hormones

Virtually all of the effects of pregnancy can be attributed in some way to the influence of hormones—particularly estrogens, progesterone, and hCG. During weeks 7–12 from the LMP, the pregnancy hormones are primarily generated by the corpus luteum. Progesterone secreted by the corpus luteum stimulates the production of decidual cells of the endometrium that nourish the blastocyst before placentation. As the placenta develops and the corpus luteum degenerates during weeks 12–17, the placenta gradually takes over as the endocrine organ of pregnancy.

The placenta converts weak androgens secreted by the maternal and fetal adrenal glands to estrogens, which are necessary for pregnancy to progress. Estrogen levels climb throughout the pregnancy, increasing 30-fold by childbirth. Estrogens have the following actions:

- They suppress FSH and LH production, effectively preventing ovulation. (This function is the biological basis of hormonal birth control pills.)
- They induce the growth of fetal tissues and are necessary for the maturation of the fetal lungs and liver.
- They promote fetal viability by regulating progesterone production and triggering fetal synthesis of cortisol, which helps with the maturation of the lungs, liver, and endocrine organs such as the thyroid gland and adrenal gland.
- They stimulate maternal tissue growth, leading to uterine enlargement and mammary duct expansion and branching.

Relaxin, another hormone secreted by the corpus luteum and then by the placenta, helps prepare the mother's body for childbirth. It increases the elasticity of the symphysis pubis joint and pelvic ligaments, making room for the growing fetus and allowing expansion of the pelvic outlet for childbirth. Relaxin also helps dilate the cervix during labor.

The placenta takes over the synthesis and secretion of progesterone throughout pregnancy as the corpus luteum degenerates. Like estrogen, progesterone suppresses FSH and LH. It also inhibits uterine contractions, protecting the fetus from preterm birth. This hormone decreases in late gestation, allowing uterine contractions to intensify and eventually progress to true labor. The placenta also produces hCG. In addition to promoting survival of the corpus luteum, hCG stimulates the male fetal gonads to secrete testosterone, which is essential for the development of the male reproductive system.

The anterior pituitary enlarges and ramps up its hormone production during pregnancy, raising the levels of thyrotropin, prolactin, and adrenocorticotropic hormone (ACTH). Thyrotropin, in conjunction with placental hormones, increases the production of thyroid hormone, which raises the maternal metabolic rate. This can markedly augment a pregnant woman's appetite and cause hot flashes. Prolactin stimulates enlargement of the mammary glands in preparation for milk production. ACTH stimulates maternal cortisol secretion, which contributes to fetal protein synthesis. In addition to the pituitary hormones, increased parathyroid levels mobilize calcium from maternal bones for fetal use.

## Weight Gain

The second and third trimesters of pregnancy are associated with dramatic changes in maternal anatomy and physiology. The most obvious anatomical sign of pregnancy is the dramatic enlargement of the abdominal region, coupled with maternal weight gain. This weight results from the growing fetus as well as the enlarged uterus, amniotic fluid, and placenta. Additional breast tissue and dramatically increased blood volume also contribute to weight gain (Table 28.2). Surprisingly, fat storage accounts for only approximately 2.3 kg (5 lbs) in a normal pregnancy and serves as a reserve for the increased metabolic demand of breastfeeding.

During the first trimester, the mother does not need to consume additional calories to maintain a healthy pregnancy. However, a weight gain of approximately 0.45 kg (1 lb) per month is common. During the second and third trimesters, the mother's appetite increases, but it is only necessary for her to consume an additional 300 calories per day to support the growing fetus. Most women gain approximately 0.45 kg (1 lb) per week.

### Contributors to Weight Gain During Pregnancy

| Component | Weight (kg) | Weight (lb) |
|---|---|---|
| Fetus | 3.2–3.6 | 7–8 |
| Placenta and fetal membranes | 0.9–1.8 | 2–4 |
| Amniotic fluid | 0.9–1.4 | 2–3 |
| Breast tissue | 0.9–1.4 | 2–3 |
| Blood | 1.4 | 4 |
| Fat | 0.9–4.1 | 3–9 |
| Uterus | 0.9–2.3 | 2–5 |
| Total | 10–16.3 | 22–36 |

Table 28.2

## Changes in Organ Systems During Pregnancy

As the woman's body adapts to pregnancy, characteristic physiologic changes occur. These changes can sometimes prompt symptoms often referred to collectively as the common discomforts of pregnancy.

### Digestive and Urinary System Changes

Nausea and vomiting, sometimes triggered by an increased sensitivity to odors, are common during the first few weeks to months of pregnancy. This phenomenon is often referred to as "morning sickness," although the nausea may persist all day. The source of pregnancy nausea is thought to be the increased circulation of pregnancy-related hormones, specifically circulating estrogen, progesterone, and hCG. Decreased intestinal peristalsis may also contribute to nausea. By about week 12 of pregnancy, nausea typically subsides.

A common gastrointestinal complaint during the later stages of pregnancy is gastric reflux, or heartburn, which results from the upward, constrictive pressure of the growing uterus on the stomach. The same decreased peristalsis that may contribute to nausea in early pregnancy is also thought to be responsible for pregnancy-related constipation as pregnancy progresses.

The downward pressure of the uterus also compresses the urinary bladder, leading to frequent urination. The problem is exacerbated by increased urine production. In addition, the maternal urinary system processes both maternal and fetal wastes, further increasing the total volume of urine.

### Circulatory System Changes

Blood volume increases substantially during pregnancy, so that by childbirth, it exceeds its preconception volume by 30 percent, or approximately 1–2 liters. The greater blood volume helps to manage the demands of fetal nourishment and fetal waste removal. In conjunction with increased blood volume, the pulse and blood pressure also rise moderately during pregnancy. As the fetus grows, the uterus compresses underlying pelvic blood vessels, hampering venous return from the legs and pelvic region. As a result, many pregnant women develop varicose veins or hemorrhoids.

### Respiratory System Changes

During the second half of pregnancy, the respiratory minute volume (volume of gas inhaled or exhaled by the lungs per minute) increases by 50 percent to compensate for the oxygen demands of the fetus and the increased maternal metabolic rate. The growing uterus exerts upward pressure on the diaphragm, decreasing the volume of each inspiration and potentially

causing shortness of breath, or dyspnea. During the last several weeks of pregnancy, the pelvis becomes more elastic, and the fetus descends lower in a process called **lightening**. This typically ameliorates dyspnea.

The respiratory mucosa swell in response to increased blood flow during pregnancy, leading to nasal congestion and nose bleeds, particularly when the weather is cold and dry. Humidifier use and increased fluid intake are often recommended to counteract congestion.

### Integumentary System Changes

The dermis stretches extensively to accommodate the growing uterus, breast tissue, and fat deposits on the thighs and hips. Torn connective tissue beneath the dermis can cause striae (stretch marks) on the abdomen, which appear as red or purple marks during pregnancy that fade to a silvery white color in the months after childbirth.

An increase in melanocyte-stimulating hormone, in conjunction with estrogens, darkens the areolae and creates a line of pigment from the umbilicus to the pubis called the linea nigra (**Figure 28.19**). Melanin production during pregnancy may also darken or discolor skin on the face to create a chloasma, or “mask of pregnancy.”

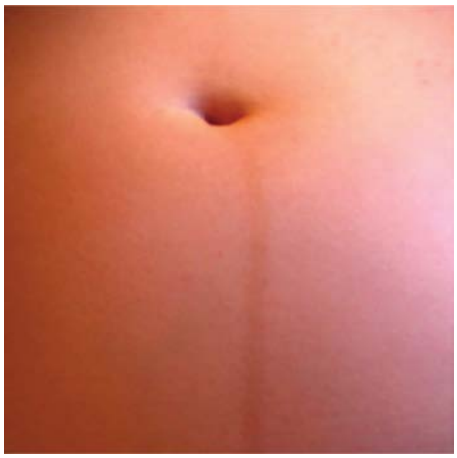


**Figure 28.19 Linea Nigra** The linea nigra, a dark medial line running from the umbilicus to the pubis, forms during pregnancy and persists for a few weeks following childbirth. The linea nigra shown here corresponds to a pregnancy that is 22 weeks along.

## Physiology of Labor

Childbirth, or **parturition**, typically occurs within a week of a woman’s due date, unless the woman is pregnant with more than one fetus, which usually causes her to go into labor early. As a pregnancy progresses into its final weeks, several physiological changes occur in response to hormones that trigger labor.

First, recall that progesterone inhibits uterine contractions throughout the first several months of pregnancy. As the pregnancy enters its seventh month, progesterone levels plateau and then drop. Estrogen levels, however, continue to rise in the maternal circulation (**Figure 28.20**). The increasing ratio of estrogen to progesterone makes the myometrium (the uterine smooth muscle) more sensitive to stimuli that promote contractions (because progesterone no longer inhibits them). Moreover, in the eighth month of pregnancy, fetal cortisol rises, which boosts estrogen secretion by the placenta and further overpowers the uterine-calming effects of progesterone. Some women may feel the result of the decreasing levels of progesterone in late pregnancy as weak and irregular peristaltic **Braxton Hicks contractions**, also called false labor. These contractions can often be relieved with rest or hydration.

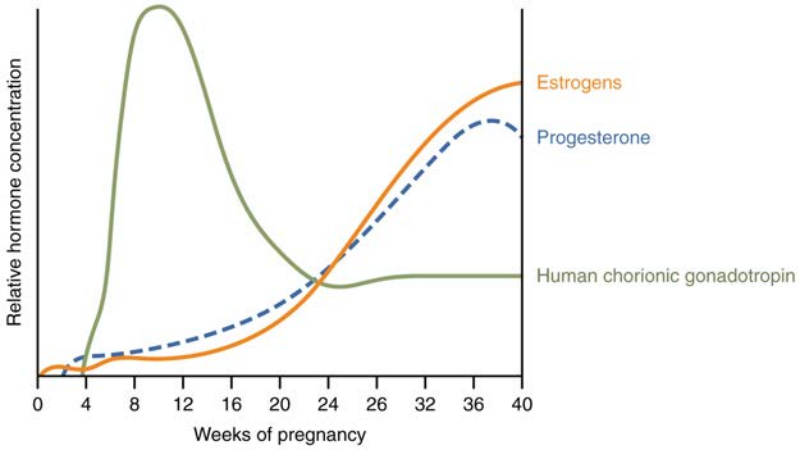



**Figure 28.20 Hormones Initiating Labor** A positive feedback loop of hormones works to initiate labor.

A common sign that labor will be short is the so-called "bloody show." During pregnancy, a plug of mucus accumulates in the cervical canal, blocking the entrance to the uterus. Approximately 1–2 days prior to the onset of true labor, this plug loosens and is expelled, along with a small amount of blood.

Meanwhile, the posterior pituitary has been boosting its secretion of oxytocin, a hormone that stimulates the contractions of labor. At the same time, the myometrium increases its sensitivity to oxytocin by expressing more receptors for this hormone. As labor nears, oxytocin begins to stimulate stronger, more painful uterine contractions, which—in a positive feedback loop—stimulate the secretion of prostaglandins from fetal membranes. Like oxytocin, prostaglandins also enhance uterine contractile strength. The fetal pituitary also secretes oxytocin, which increases prostaglandins even further. Given the importance of oxytocin and prostaglandins to the initiation and maintenance of labor, it is not surprising that, when a pregnancy is not progressing to labor and needs to be induced, a pharmaceutical version of these compounds (called pitocin) is administered by intravenous drip.

Finally, stretching of the myometrium and cervix by a full-term fetus in the vertex (head-down) position is regarded as a stimulant to uterine contractions. The sum of these changes initiates the regular contractions known as **true labor**, which become more powerful and more frequent with time. The pain of labor is attributed to myometrial hypoxia during uterine contractions.

## Stages of Childbirth

The process of childbirth can be divided into three stages: cervical dilation, expulsion of the newborn, and afterbirth (**Figure 28.21**).

### Cervical Dilation

For vaginal birth to occur, the cervix must dilate fully to 10 cm in diameter—wide enough to deliver the newborn's head. The **dilation** stage is the longest stage of labor and typically takes 6–12 hours. However, it varies widely and may take minutes, hours, or days, depending in part on whether the mother has given birth before; in each subsequent labor, this stage tends to be shorter.

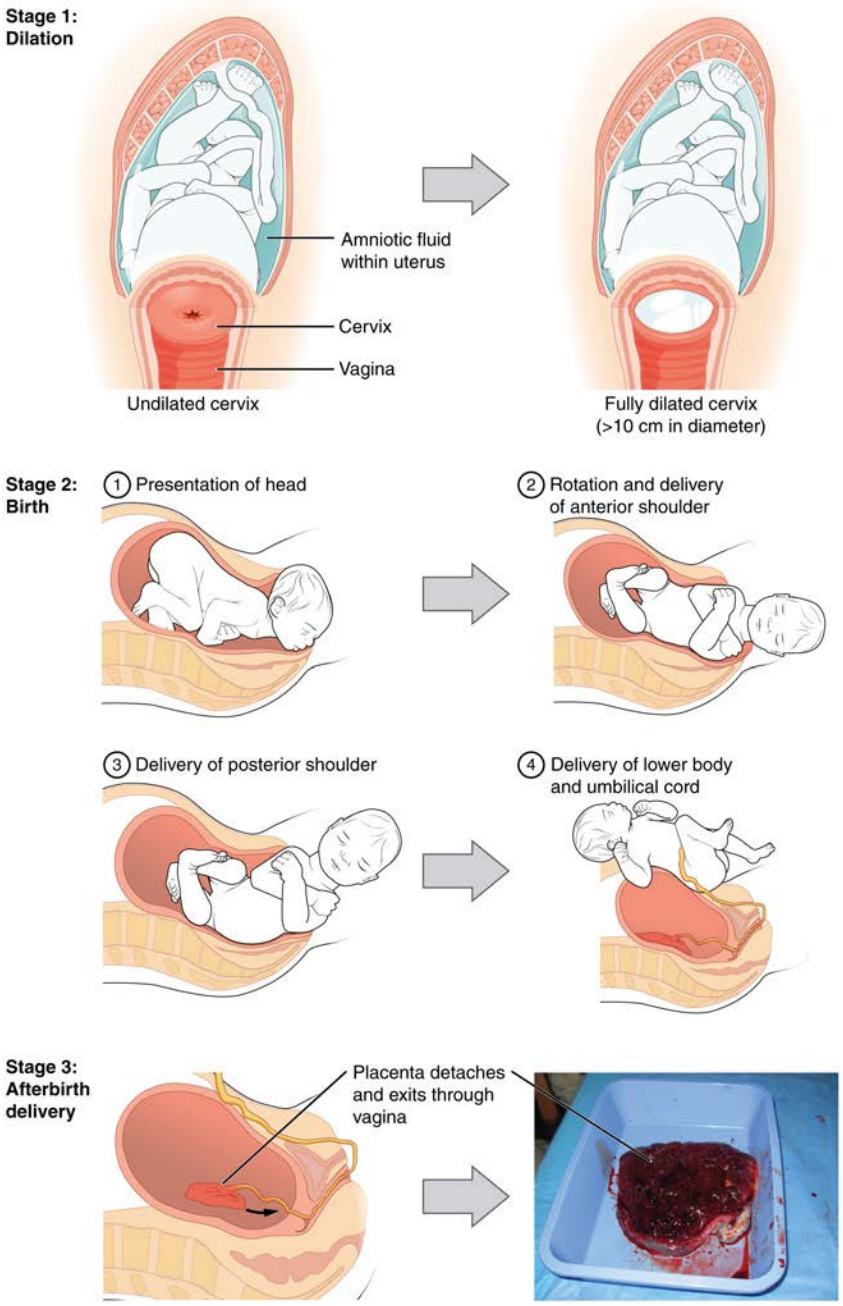



**Figure 28.21 Stages of Childbirth** The stages of childbirth include Stage 1, early cervical dilation; Stage 2, full dilation and expulsion of the newborn; and Stage 3, delivery of the placenta and associated fetal membranes. (The position of the newborn's shoulder is described relative to the mother.)

True labor progresses in a positive feedback loop in which uterine contractions stretch the cervix, causing it to dilate and efface, or become thinner. Cervical stretching induces reflexive uterine contractions that dilate and efface the cervix further. In addition, cervical dilation boosts oxytocin secretion from the pituitary, which in turn triggers more powerful uterine contractions. When labor begins, uterine contractions may occur only every 3–30 minutes and last only 20–40 seconds; however, by the end of this stage, contractions may occur as frequently as every 1.5–2 minutes and last for a full minute.

Each contraction sharply reduces oxygenated blood flow to the fetus. For this reason, it is critical that a period of relaxation occur after each contraction. Fetal distress, measured as a sustained decrease or increase in the fetal heart rate, can result from severe contractions that are too powerful or lengthy for oxygenated blood to be restored to the fetus. Such a situation can be cause for an emergency birth with vacuum, forceps, or surgically by Caesarian section.

The amniotic membranes rupture before the onset of labor in about 12 percent of women; they typically rupture at the end of the dilation stage in response to excessive pressure from the fetal head entering the birth canal.

### Expulsion Stage

The **expulsion** stage begins when the fetal head enters the birth canal and ends with birth of the newborn. It typically takes up to 2 hours, but it can last longer or be completed in minutes, depending in part on the orientation of the fetus. The vertex presentation known as the occiput anterior vertex is the most common presentation and is associated with the greatest ease of vaginal birth. The fetus faces the maternal spinal cord and the smallest part of the head (the posterior aspect called the occiput) exits the birth canal first.

In fewer than 5 percent of births, the infant is oriented in the breech presentation, or buttocks down. In a complete breech, both legs are crossed and oriented downward. In a frank breech presentation, the legs are oriented upward. Before the 1960s, it was common for breech presentations to be delivered vaginally. Today, most breech births are accomplished by Caesarian section.

Vaginal birth is associated with significant stretching of the vaginal canal, the cervix, and the perineum. Until recent decades, it was routine procedure for an obstetrician to numb the perineum and perform an **episiotomy**, an incision in the posterior vaginal wall and perineum. The perineum is now more commonly allowed to tear on its own during birth. Both an episiotomy and a perineal tear need to be sutured shortly after birth to ensure optimal healing. Although suturing the jagged edges of a perineal tear may be more difficult than suturing an episiotomy, tears heal more quickly, are less painful, and are associated with less damage to the muscles around the vagina and rectum.

Upon birth of the newborn's head, an obstetrician will aspirate mucus from the mouth and nose before the newborn's first breath. Once the head is birthed, the rest of the body usually follows quickly. The umbilical cord is then double-clamped, and a cut is made between the clamps. This completes the second stage of childbirth.

### Afterbirth

The delivery of the placenta and associated membranes, commonly referred to as the **afterbirth**, marks the final stage of childbirth. After expulsion of the newborn, the myometrium continues to contract. This movement shears the placenta from the back of the uterine wall. It is then easily delivered through the vagina. Continued uterine contractions then reduce blood loss from the site of the placenta. Delivery of the placenta marks the beginning of the postpartum period—the period of approximately 6 weeks immediately following childbirth during which the mother's body gradually returns to a non-pregnant state. If the placenta does not birth spontaneously within approximately 30 minutes, it is considered retained, and the obstetrician may attempt manual removal. If this is not successful, surgery may be required.

It is important that the obstetrician examines the expelled placenta and fetal membranes to ensure that they are intact. If fragments of the placenta remain in the uterus, they can cause postpartum hemorrhage. Uterine contractions continue for several hours after birth to return the uterus to its pre-pregnancy size in a process called **involution**, which also allows the mother's abdominal organs to return to their pre-pregnancy locations. Breastfeeding facilitates this process.

Although postpartum uterine contractions limit blood loss from the detachment of the placenta, the mother does experience a postpartum vaginal discharge called **lochia**. This is made up of uterine lining cells, erythrocytes, leukocytes, and other debris. Thick, dark, lochia rubra (red lochia) typically continues for 2–3 days, and is replaced by lochia serosa, a thinner, pinkish form that continues until about the tenth postpartum day. After this period, a scant, creamy, or watery discharge called lochia alba (white lochia) may continue for another 1–2 weeks.

## 28.5 | Adjustments of the Infant at Birth and Postnatal Stages

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

- Discuss the importance of an infant's first breath
- Explain the closing of the cardiac shunts
- Describe thermoregulation in the newborn
- Summarize the importance of intestinal flora in the newborn

From a fetal perspective, the process of birth is a crisis. In the womb, the fetus was snuggled in a soft, warm, dark, and quiet world. The placenta provided nutrition and oxygen continuously. Suddenly, the contractions of labor and vaginal childbirth forcibly squeeze the fetus through the birth canal, limiting oxygenated blood flow during contractions and shifting the skull bones to accommodate the small space. After birth, the newborn's system must make drastic adjustments to a world that is colder, brighter, and louder, and where he or she will experience hunger and thirst. The neonatal period (neo- = "new"; -natal = "birth") spans the first to the thirtieth day of life outside of the uterus.

### Respiratory Adjustments

Although the fetus "practices" breathing by inhaling amniotic fluid in utero, there is no air in the uterus and thus no true opportunity to breathe. (There is also no need to breathe because the placenta supplies the fetus with all the oxygenated blood it needs.) During gestation, the partially collapsed lungs are filled with amniotic fluid and exhibit very little metabolic

activity. Several factors stimulate newborns to take their first breath at birth. First, labor contractions temporarily constrict umbilical blood vessels, reducing oxygenated blood flow to the fetus and elevating carbon dioxide levels in the blood. High carbon dioxide levels cause acidosis and stimulate the respiratory center in the brain, triggering the newborn to take a breath.

The first breath typically is taken within 10 seconds of birth, after mucus is aspirated from the infant's mouth and nose. The first breaths inflate the lungs to nearly full capacity and dramatically decrease lung pressure and resistance to blood flow, causing a major circulatory reconfiguration. Pulmonary alveoli open, and alveolar capillaries fill with blood. Amniotic fluid in the lungs drains or is absorbed, and the lungs immediately take over the task of the placenta, exchanging carbon dioxide for oxygen by the process of respiration.

## Circulatory Adjustments

The process of clamping and cutting the umbilical cord collapses the umbilical blood vessels. In the absence of medical assistance, this occlusion would occur naturally within 20 minutes of birth because the Wharton's jelly within the umbilical cord would swell in response to the lower temperature outside of the mother's body, and the blood vessels would constrict. Natural occlusion has occurred when the umbilical cord is no longer pulsating. For the most part, the collapsed vessels atrophy and become fibrotic remnants, existing in the mature circulatory system as ligaments of the abdominal wall and liver. The ductus venosus degenerates to become the ligamentum venosum beneath the liver. Only the proximal sections of the two umbilical arteries remain functional, taking on the role of supplying blood to the upper part of the bladder (**Figure 28.22**).

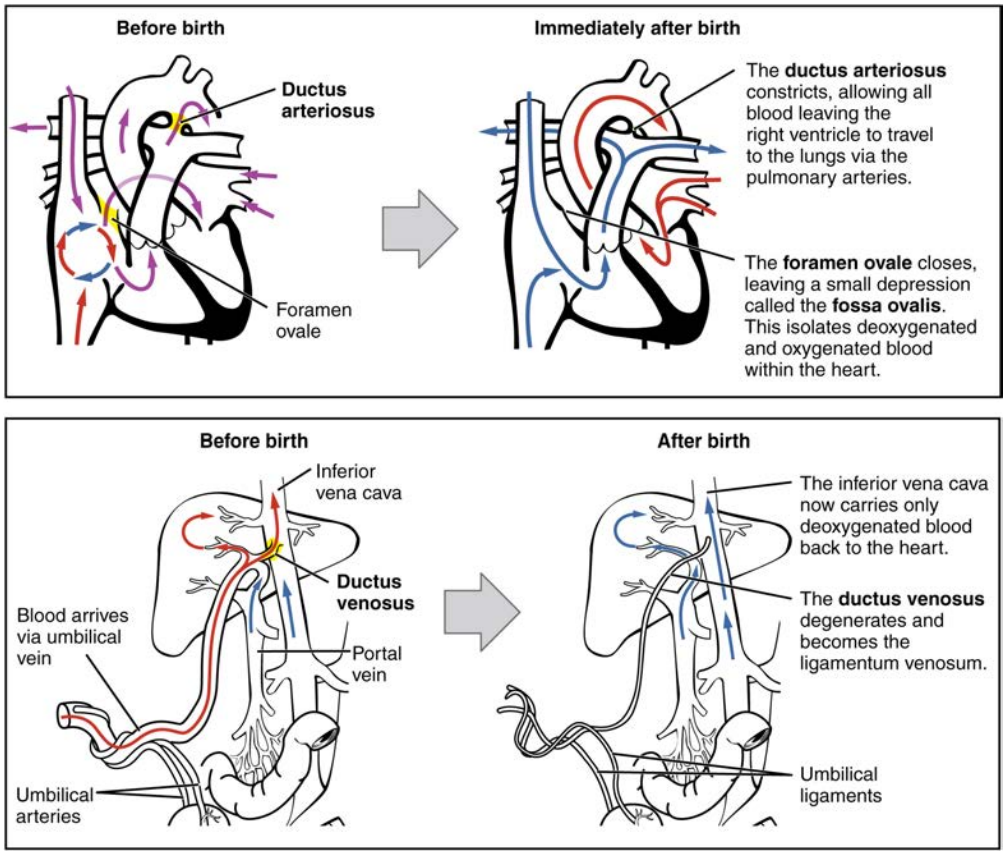



**Figure 28.22 Neonatal Circulatory System** A newborn's circulatory system reconfigures immediately after birth. The three fetal shunts have been closed permanently, facilitating blood flow to the liver and lungs.

The newborn's first breath is vital to initiate the transition from the fetal to the neonatal circulatory pattern. Inflation of the lungs decreases blood pressure throughout the pulmonary system, as well as in the right atrium and ventricle. In response to this pressure change, the flow of blood temporarily reverses direction through the foramen ovale, moving from the left to the right atrium, and blocking the shunt with two flaps of tissue. Within 1 year, the tissue flaps usually fuse over the shunt, turning the foramen ovale into the fossa ovalis. The ductus arteriosus constricts as a result of increased oxygen concentration, and becomes the ligamentum arteriosum. Closing of the ductus arteriosus ensures that all blood pumped to the pulmonary circuit will be oxygenated by the newly functional neonatal lungs.

## Thermoregulatory Adjustments

The fetus floats in warm amniotic fluid that is maintained at a temperature of approximately 98.6°F with very little fluctuation. Birth exposes newborns to a cooler environment in which they have to regulate their own body temperature.

Newborns have a higher ratio of surface area to volume than adults. This means that their body has less volume throughout which to produce heat, and more surface area from which to lose heat. As a result, newborns produce heat more slowly and lose it more quickly. Newborns also have immature musculature that limits their ability to generate heat by shivering. Moreover, their nervous systems are underdeveloped, so they cannot quickly constrict superficial blood vessels in response to cold. They also have little subcutaneous fat for insulation. All these factors make it harder for newborns to maintain their body temperature.

Newborns, however, do have a special method for generating heat: **nonshivering thermogenesis**, which involves the breakdown of **brown adipose tissue**, or brown fat, which is distributed over the back, chest, and shoulders. Brown fat differs from the more familiar white fat in two ways:

- It is highly vascularized. This allows for faster delivery of oxygen, which leads to faster cellular respiration.
- It is packed with a special type of mitochondria that are able to engage in cellular respiration reactions that produce less ATP and more heat than standard cellular respiration reactions.

The breakdown of brown fat occurs automatically upon exposure to cold, so it is an important heat regulator in newborns. During fetal development, the placenta secretes inhibitors that prevent metabolism of brown adipose fat and promote its accumulation in preparation for birth.

### Gastrointestinal and Urinary Adjustments

In adults, the gastrointestinal tract harbors bacterial flora—trillions of bacteria that aid in digestion, produce vitamins, and protect from the invasion or replication of pathogens. In stark contrast, the fetal intestine is sterile. The first consumption of breast milk or formula floods the neonatal gastrointestinal tract with beneficial bacteria that begin to establish the bacterial flora.

The fetal kidneys filter blood and produce urine, but the neonatal kidneys are still immature and inefficient at concentrating urine. Therefore, newborns produce very dilute urine, making it particularly important for infants to obtain sufficient fluids from breast milk or formula.

## Homeostatic IMBALANCES

### Homeostasis in the Newborn: Apgar Score

In the minutes following birth, a newborn must undergo dramatic systemic changes to be able to survive outside the womb. An obstetrician, midwife, or nurse can estimate how well a newborn is doing by obtaining an Apgar score. The Apgar score was introduced in 1952 by the anesthesiologist Dr. Virginia Apgar as a method to assess the effects on the newborn of anesthesia given to the laboring mother. Healthcare providers now use it to assess the general wellbeing of the newborn, whether or not analgesics or anesthetics were used.

Five criteria—skin color, heart rate, reflex, muscle tone, and respiration—are assessed, and each criterion is assigned a score of 0, 1, or 2. Scores are taken at 1 minute after birth and again at 5 minutes after birth. Each time that scores are taken, the five scores are added together. High scores (out of a possible 10) indicate the baby has made the transition from the womb well, whereas lower scores indicate that the baby may be in distress.

The technique for determining an Apgar score is quick and easy, painless for the newborn, and does not require any instruments except for a stethoscope. A convenient way to remember the five scoring criteria is to apply the mnemonic APGAR, for “appearance” (skin color), “pulse” (heart rate), “grimace” (reflex), “activity” (muscle tone), and “respiration.”

Of the five Apgar criteria, heart rate and respiration are the most critical. Poor scores for either of these measurements may indicate the need for immediate medical attention to resuscitate or stabilize the newborn. In general, any score lower than 7 at the 5-minute mark indicates that medical assistance may be needed. A total score below 5 indicates an emergency situation. Normally, a newborn will get an intermediate score of 1 for some of the Apgar criteria and will progress to a 2 by the 5-minute assessment. Scores of 8 or above are normal.

# 28.6 | Lactation

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

- Describe the structure of the lactating breast
- Summarize the process of lactation
- Explain how the composition of breast milk changes during the first days of lactation and in the course of a single feeding

**Lactation** is the process by which milk is synthesized and secreted from the mammary glands of the postpartum female breast in response to an infant sucking at the nipple. Breast milk provides ideal nutrition and passive immunity for the infant, encourages mild uterine contractions to return the uterus to its pre-pregnancy size (i.e., involution), and induces a substantial metabolic increase in the mother, consuming the fat reserves stored during pregnancy.

## Structure of the Lactating Breast

Mammary glands are modified sweat glands. The non-pregnant and non-lactating female breast is composed primarily of adipose and collagenous tissue, with mammary glands making up a very minor proportion of breast volume. The mammary gland is composed of milk-transporting lactiferous ducts, which expand and branch extensively during pregnancy in response to estrogen, growth hormone, cortisol, and prolactin. Moreover, in response to progesterone, clusters of breast alveoli bud from the ducts and expand outward toward the chest wall. Breast alveoli are balloon-like structures lined with milk-secreting cuboidal cells, or lactocytes, that are surrounded by a net of contractile myoepithelial cells. Milk is secreted from the lactocytes, fills the alveoli, and is squeezed into the ducts. Clusters of alveoli that drain to a common duct are called lobules; the lactating female has 12–20 lobules organized radially around the nipple. Milk drains from lactiferous ducts into lactiferous sinuses that meet at 4 to 18 perforations in the nipple, called nipple pores. The small bumps of the areola (the darkened skin around the nipple) are called Montgomery glands. They secrete oil to cleanse the nipple opening and prevent chapping and cracking of the nipple during breastfeeding.

## The Process of Lactation

The pituitary hormone **prolactin** is instrumental in the establishment and maintenance of breast milk supply. It also is important for the mobilization of maternal micronutrients for breast milk.

Near the fifth week of pregnancy, the level of circulating prolactin begins to increase, eventually rising to approximately 10–20 times the pre-pregnancy concentration. We noted earlier that, during pregnancy, prolactin and other hormones prepare the breasts anatomically for the secretion of milk. The level of prolactin plateaus in late pregnancy, at a level high enough to initiate milk production. However, estrogen, progesterone, and other placental hormones inhibit prolactin-mediated milk synthesis during pregnancy. It is not until the placenta is expelled that this inhibition is lifted and milk production commences.

After childbirth, the baseline prolactin level drops sharply, but it is restored for a 1-hour spike during each feeding to stimulate the production of milk for the next feeding. With each prolactin spike, estrogen and progesterone also increase slightly.

When the infant suckles, sensory nerve fibers in the areola trigger a neuroendocrine reflex that results in milk secretion from lactocytes into the alveoli. The posterior pituitary releases oxytocin, which stimulates myoepithelial cells to squeeze milk from the alveoli so it can drain into the lactiferous ducts, collect in the lactiferous sinuses, and discharge through the nipple pores. It takes less than 1 minute from the time when an infant begins suckling (the latent period) until milk is secreted (the let-down). **Figure 28.23** summarizes the positive feedback loop of the **let-down reflex**.

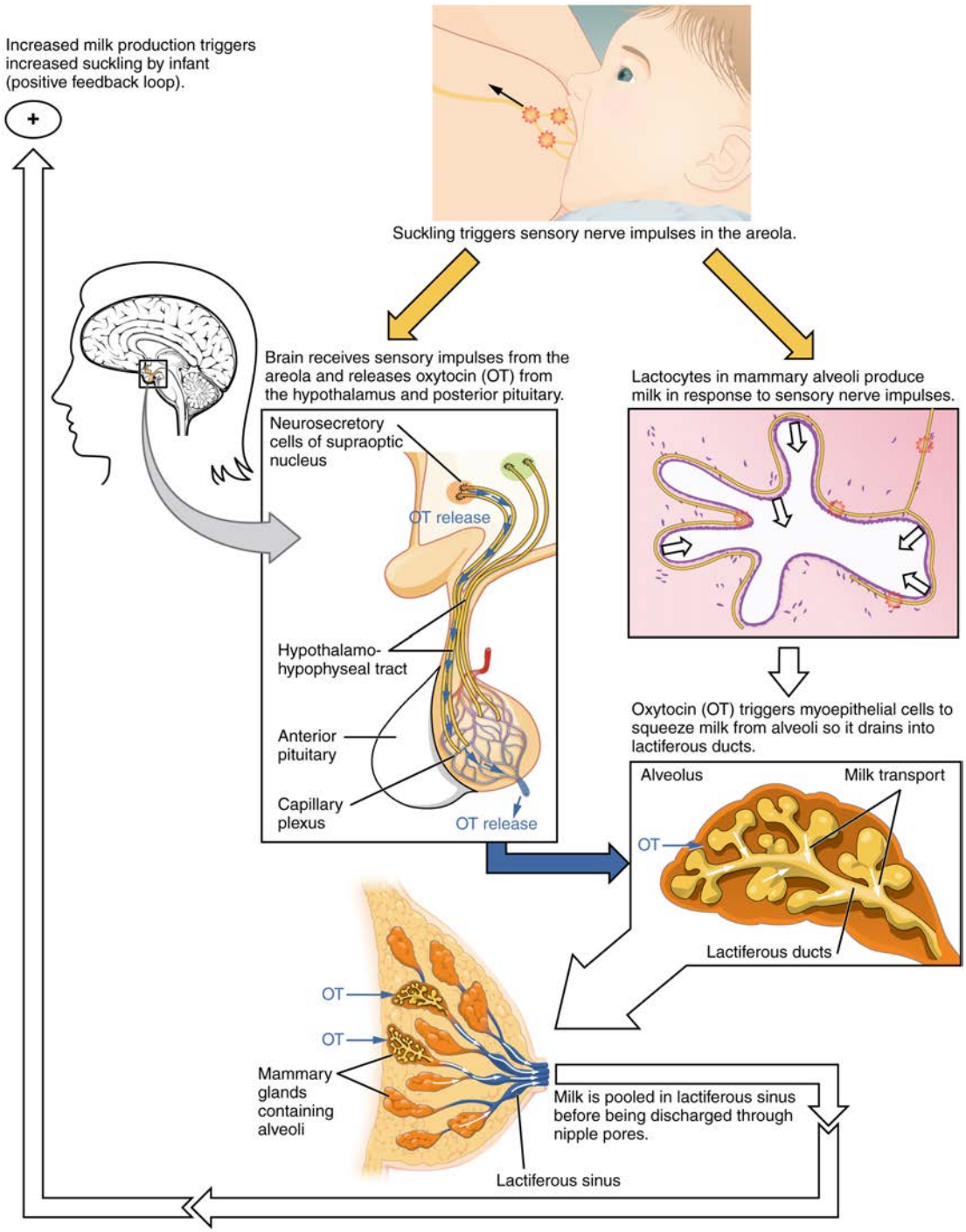



**Figure 28.23 Let-Down Reflex** A positive feedback loop ensures continued milk production as long as the infant continues to breastfeed.

The prolactin-mediated synthesis of milk changes with time. Frequent milk removal by breastfeeding (or pumping) will maintain high circulating prolactin levels for several months. However, even with continued breastfeeding, baseline prolactin will decrease over time to its pre-pregnancy level. In addition to prolactin and oxytocin, growth hormone, cortisol, parathyroid hormone, and insulin contribute to lactation, in part by facilitating the transport of maternal amino acids, fatty acids, glucose, and calcium to breast milk.

## Changes in the Composition of Breast Milk

In the final weeks of pregnancy, the alveoli swell with **colostrum**, a thick, yellowish substance that is high in protein but contains less fat and glucose than mature breast milk (Table 28.3). Before childbirth, some women experience leakage of colostrum from the nipples. In contrast, mature breast milk does not leak during pregnancy and is not secreted until several days after childbirth.

**Compositions of Human Colostrum, Mature Breast Milk, and Cow's Milk (g/L)**

| | Human colostrum | Human breast milk | Cow's milk* |
|---|---|---|---|
| **Total protein** | 23 | 11 | 31 |
| **Immunoglobulins** | 19 | 0.1 | 1 |
| **Fat** | 30 | 45 | 38 |
| **Lactose** | 57 | 71 | 47 |
| **Calcium** | 0.5 | 0.3 | 1.4 |
| **Phosphorus** | 0.16 | 0.14 | 0.90 |
| **Sodium** | 0.50 | 0.15 | 0.41 |

**Table 28.3 *Cow's milk should never be given to an infant. Its composition is not suitable and its proteins are difficult for the infant to digest.**

Colostrum is secreted during the first 48–72 hours postpartum. Only a small volume of colostrum is produced—approximately 3 ounces in a 24-hour period—but it is sufficient for the newborn in the first few days of life. Colostrum is rich with immunoglobulins, which confer gastrointestinal, and also likely systemic, immunity as the newborn adjusts to a nonsterile environment.

After about the third postpartum day, the mother secretes transitional milk that represents an intermediate between mature milk and colostrum. This is followed by mature milk from approximately postpartum day 10 (see **Table 28.3**). As you can see in the accompanying table, cow's milk is not a substitute for breast milk. It contains less lactose, less fat, and more protein and minerals. Moreover, the proteins in cow's milk are difficult for an infant's immature digestive system to metabolize and absorb.

The first few weeks of breastfeeding may involve leakage, soreness, and periods of milk engorgement as the relationship between milk supply and infant demand becomes established. Once this period is complete, the mother will produce approximately 1.5 liters of milk per day for a single infant, and more if she has twins or triplets. As the infant goes through growth spurts, the milk supply constantly adjusts to accommodate changes in demand. A woman can continue to lactate for years, but once breastfeeding is stopped for approximately 1 week, any remaining milk will be reabsorbed; in most cases, no more will be produced, even if suckling or pumping is resumed.

Mature milk changes from the beginning to the end of a feeding. The early milk, called **foremilk**, is watery, translucent, and rich in lactose and protein. Its purpose is to quench the infant's thirst. **Hindmilk** is delivered toward the end of a feeding. It is opaque, creamy, and rich in fat, and serves to satisfy the infant's appetite.

During the first days of a newborn's life, it is important for meconium to be cleared from the intestines and for bilirubin to be kept low in the circulation. Recall that bilirubin, a product of erythrocyte breakdown, is processed by the liver and secreted in bile. It enters the gastrointestinal tract and exits the body in the stool. Breast milk has laxative properties that help expel meconium from the intestines and clear bilirubin through the excretion of bile. A high concentration of bilirubin in the blood causes jaundice. Some degree of jaundice is normal in newborns, but a high level of bilirubin—which is neurotoxic—can cause brain damage. Newborns, who do not yet have a fully functional blood–brain barrier, are highly vulnerable to the bilirubin circulating in the blood. Indeed, hyperbilirubinemia, a high level of circulating bilirubin, is the most common condition requiring medical attention in newborns. Newborns with hyperbilirubinemia are treated with phototherapy because UV light helps to break down the bilirubin quickly.

## 28.7 | Patterns of Inheritance

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

- Differentiate between genotype and phenotype
- Describe how alleles determine a person's traits
- Summarize Mendel's experiments and relate them to human genetics
- Explain the inheritance of autosomal dominant and recessive and sex-linked genetic disorders

We have discussed the events that lead to the development of a newborn. But what makes each newborn unique? The answer lies, of course, in the DNA in the sperm and oocyte that combined to produce that first diploid cell, the human zygote.

## From Genotype to Phenotype

Each human body cell has a full complement of DNA stored in 23 pairs of chromosomes. **Figure 28.24** shows the pairs in a systematic arrangement called a **karyotype**. Among these is one pair of chromosomes, called the **sex chromosomes**, that determines the sex of the individual (XX in females, XY in males). The remaining 22 chromosome pairs are called **autosomal chromosomes**. Each of these chromosomes carries hundreds or even thousands of genes, each of which codes for the assembly of a particular protein—that is, genes are "expressed" as proteins. An individual's complete genetic makeup is referred to as his or her **genotype**. The characteristics that the genes express, whether they are physical, behavioral, or biochemical, are a person's **phenotype**.

You inherit one chromosome in each pair—a full complement of 23—from each parent. This occurs when the sperm and oocyte combine at the moment of your conception. Homologous chromosomes—those that make up a complementary pair—have genes for the same characteristics in the same location on the chromosome. Because one copy of a gene, an **allele**, is inherited from each parent, the alleles in these complementary pairs may vary. Take for example an allele that encodes for dimples. A child may inherit the allele encoding for dimples on the chromosome from the father and the allele that encodes for smooth skin (no dimples) on the chromosome from the mother.

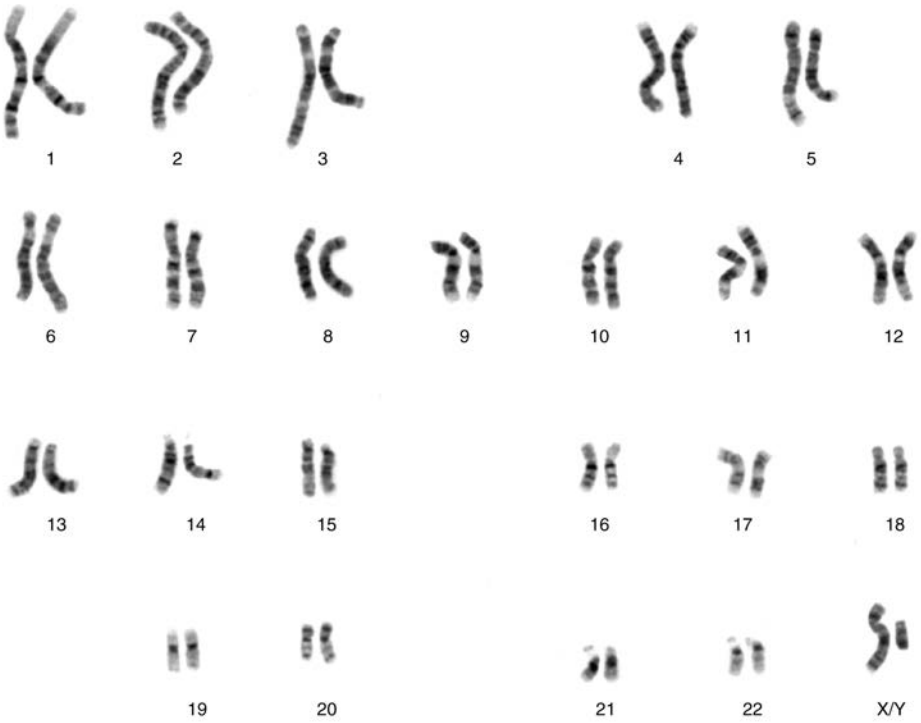



**Figure 28.24 Chromosomal Complement of a Male** Each pair of chromosomes contains hundreds to thousands of genes. The banding patterns are nearly identical for the two chromosomes within each pair, indicating the same organization of genes. As is visible in this karyotype, the only exception to this is the XY sex chromosome pair in males. (credit: National Human Genome Research Institute)

Although a person can have two identical alleles for a single gene (a **homozygous** state), it is also possible for a person to have two different alleles (a **heterozygous** state). The two alleles can interact in several different ways. The expression of an allele can be dominant, for which the activity of this gene will mask the expression of a nondominant, or recessive, allele. Sometimes dominance is complete; at other times, it is incomplete. In some cases, both alleles are expressed at the same time in a form of expression known as codominance.

In the simplest scenario, a single pair of genes will determine a single heritable characteristic. However, it is quite common for multiple genes to interact to confer a feature. For instance, eight or more genes—each with their own alleles—determine eye color in humans. Moreover, although any one person can only have two alleles corresponding to a given gene, more than two alleles commonly exist in a population. This phenomenon is called multiple alleles. For example, there are three different alleles that encode ABO blood type; these are designated $I^A$, $I^B$, and $i$.

Over 100 years of theoretical and experimental genetics studies, and the more recent sequencing and annotation of the human genome, have helped scientists to develop a better understanding of how an individual's genotype is expressed as their phenotype. This body of knowledge can help scientists and medical professionals to predict, or at least estimate, some of the features that an offspring will inherit by examining the genotypes or phenotypes of the parents. One important application of this knowledge is to identify an individual's risk for certain heritable genetic disorders. However, most diseases have a multigenic pattern of inheritance and can also be affected by the environment, so examining the genotypes or phenotypes of a person's parents will provide only limited information about the risk of inheriting a disease. Only for a

handful of single-gene disorders can genetic testing allow clinicians to calculate the probability with which a child born to the two parents tested may inherit a specific disease.

## Mendel's Theory of Inheritance

Our contemporary understanding of genetics rests on the work of a nineteenth-century monk. Working in the mid-1800s, long before anyone knew about genes or chromosomes, Gregor Mendel discovered that garden peas transmit their physical characteristics to subsequent generations in a discrete and predictable fashion. When he mated, or crossed, two pure-breeding pea plants that differed by a certain characteristic, the first-generation offspring all looked like one of the parents. For instance, when he crossed tall and dwarf pure-breeding pea plants, all of the offspring were tall. Mendel called tallness **dominant** because it was expressed in offspring when it was present in a purebred parent. He called dwarfism **recessive** because it was masked in the offspring if one of the purebred parents possessed the dominant characteristic. Note that tallness and dwarfism are variations on the characteristic of height. Mendel called such a variation a **trait**. We now know that these traits are the expression of different alleles of the gene encoding height.

Mendel performed thousands of crosses in pea plants with differing traits for a variety of characteristics. And he repeatedly came up with the same results—among the traits he studied, one was always dominant, and the other was always recessive. (Remember, however, that this dominant–recessive relationship between alleles is not always the case; some alleles are codominant, and sometimes dominance is incomplete.)

Using his understanding of dominant and recessive traits, Mendel tested whether a recessive trait could be lost altogether in a pea lineage or whether it would resurface in a later generation. By crossing the second-generation offspring of purebred parents with each other, he showed that the latter was true: recessive traits reappeared in third-generation plants in a ratio of 3:1 (three offspring having the dominant trait and one having the recessive trait). Mendel then proposed that characteristics such as height were determined by heritable "factors" that were transmitted, one from each parent, and inherited in pairs by offspring.

In the language of genetics, Mendel's theory applied to humans says that if an individual receives two dominant alleles, one from each parent, the individual's phenotype will express the dominant trait. If an individual receives two recessive alleles, then the recessive trait will be expressed in the phenotype. Individuals who have two identical alleles for a given gene, whether dominant or recessive, are said to be homozygous for that gene (homo- = "same"). Conversely, an individual who has one dominant allele and one recessive allele is said to be heterozygous for that gene (hetero- = "different" or "other"). In this case, the dominant trait will be expressed, and the individual will be phenotypically identical to an individual who possesses two dominant alleles for the trait.

It is common practice in genetics to use capital and lowercase letters to represent dominant and recessive alleles. Using Mendel's pea plants as an example, if a tall pea plant is homozygous, it will possess two tall alleles (*TT*). A dwarf pea plant must be homozygous because its dwarfism can only be expressed when two recessive alleles are present (*tt*). A heterozygous pea plant (*Tt*) would be tall and phenotypically indistinguishable from a tall homozygous pea plant because of the dominant tall allele. Mendel deduced that a 3:1 ratio of dominant to recessive would be produced by the random segregation of heritable factors (genes) when crossing two heterozygous pea plants. In other words, for any given gene, parents are equally likely to pass down either one of their alleles to their offspring in a haploid gamete, and the result will be expressed in a dominant–recessive pattern if both parents are heterozygous for the trait.

Because of the random segregation of gametes, the laws of chance and probability come into play when predicting the likelihood of a given phenotype. Consider a cross between an individual with two dominant alleles for a trait (*AA*) and an individual with two recessive alleles for the same trait (*aa*). All of the parental gametes from the dominant individual would be *A*, and all of the parental gametes from the recessive individual would be *a* (**Figure 28.25**). All of the offspring of that second generation, inheriting one allele from each parent, would have the genotype *Aa*, and the probability of expressing the phenotype of the dominant allele would be 4 out of 4, or 100 percent.

This seems simple enough, but the inheritance pattern gets interesting when the second-generation *Aa* individuals are crossed. In this generation, 50 percent of each parent's gametes are *A* and the other 50 percent are *a*. By Mendel's principle of random segregation, the possible combinations of gametes that the offspring can receive are *AA*, *Aa*, *aA* (which is the same as *Aa*), and *aa*. Because segregation and fertilization are random, each offspring has a 25 percent chance of receiving any of these combinations. Therefore, if an *Aa* × *Aa* cross were performed 1000 times, approximately 250 (25 percent) of the offspring would be *AA*; 500 (50 percent) would be *Aa* (that is, *Aa* plus *aA*); and 250 (25 percent) would be *aa*. The genotypic ratio for this inheritance pattern is 1:2:1. However, we have already established that *AA* and *Aa* (and *aA*) individuals all express the dominant trait (i.e., share the same phenotype), and can therefore be combined into one group. The result is Mendel's third-generation phenotype ratio of 3:1.

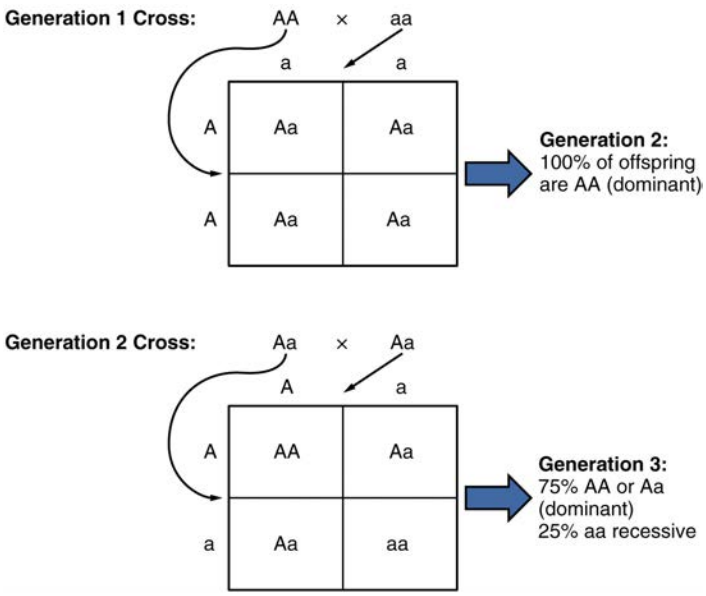



**Figure 28.25 Random Segregation** In the formation of gametes, it is equally likely that either one of a pair alleles from one parent will be passed on to the offspring. This figure follows the possible combinations of alleles through two generations following a first-generation cross of homozygous dominant and homozygous recessive parents. The recessive phenotype, which is masked in the second generation, has a 1 in 4, or 25 percent, chance of reappearing in the third generation.

Mendel's observation of pea plants also included many crosses that involved multiple traits, which prompted him to formulate the principle of independent assortment. The law states that the members of one pair of genes (alleles) from a parent will sort independently from other pairs of genes during the formation of gametes. Applied to pea plants, that means that the alleles associated with the different traits of the plant, such as color, height, or seed type, will sort independently of one another. This holds true except when two alleles happen to be located close to one other on the same chromosome. Independent assortment provides for a great degree of diversity in offspring.

Mendelian genetics represent the fundamentals of inheritance, but there are two important qualifiers to consider when applying Mendel's findings to inheritance studies in humans. First, as we've already noted, not all genes are inherited in a dominant–recessive pattern. Although all diploid individuals have two alleles for every gene, allele pairs may interact to create several types of inheritance patterns, including incomplete dominance and codominance.

Secondly, Mendel performed his studies using thousands of pea plants. He was able to identify a 3:1 phenotypic ratio in second-generation offspring because his large sample size overcame the influence of variability resulting from chance. In contrast, no human couple has ever had thousands of children. If we know that a man and woman are both heterozygous for a recessive genetic disorder, we would predict that one in every four of their children would be affected by the disease. In real life, however, the influence of chance could change that ratio significantly. For example, if a man and a woman are both heterozygous for cystic fibrosis, a recessive genetic disorder that is expressed only when the individual has two defective alleles, we would expect one in four of their children to have cystic fibrosis. However, it is entirely possible for them to have seven children, none of whom is affected, or for them to have two children, both of whom are affected. For each individual child, the presence or absence of a single gene disorder depends on which alleles that child inherits from his or her parents.

## Autosomal Dominant Inheritance

In the case of cystic fibrosis, the disorder is recessive to the normal phenotype. However, a genetic abnormality may be dominant to the normal phenotype. When the dominant allele is located on one of the 22 pairs of autosomes (non-sex chromosomes), we refer to its inheritance pattern as **autosomal dominant**. An example of an autosomal dominant disorder is neurofibromatosis type I, a disease that induces tumor formation within the nervous system that leads to skin and skeletal deformities. Consider a couple in which one parent is heterozygous for this disorder (and who therefore has neurofibromatosis), *Nn*, and one parent is homozygous for the normal gene, *nn*. The heterozygous parent would have a 50 percent chance of passing the dominant allele for this disorder to his or her offspring, and the homozygous parent would always pass the normal allele. Therefore, four possible offspring genotypes are equally likely to occur: *Nn*, *Nn*, *nn*, and *nn*. That is, every child of this couple would have a 50 percent chance of inheriting neurofibromatosis. This inheritance pattern is shown in **Figure 28.26**, in a form called a **Punnett square**, named after its creator, the British geneticist Reginald Punnett.

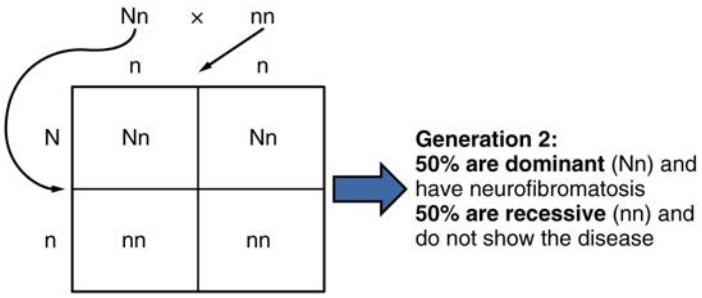



**Figure 28.26 Autosomal Dominant Inheritance** Inheritance pattern of an autosomal dominant disorder, such as neurofibromatosis, is shown in a Punnett square.

Other genetic diseases that are inherited in this pattern are achondroplastic dwarfism, Marfan syndrome, and Huntington's disease. Because autosomal dominant disorders are expressed by the presence of just one gene, an individual with the disorder will know that he or she has at least one faulty gene. The expression of the disease may manifest later in life, after the childbearing years, which is the case in Huntington's disease (discussed in more detail later in this section).

## Autosomal Recessive Inheritance

When a genetic disorder is inherited in an **autosomal recessive** pattern, the disorder corresponds to the recessive phenotype. Heterozygous individuals will not display symptoms of this disorder, because their unaffected gene will compensate. Such an individual is called a **carrier**. Carriers for an autosomal recessive disorder may never know their genotype unless they have a child with the disorder.

An example of an autosomal recessive disorder is cystic fibrosis (CF), which we introduced earlier. CF is characterized by the chronic accumulation of a thick, tenacious mucus in the lungs and digestive tract. Decades ago, children with CF rarely lived to adulthood. With advances in medical technology, the average lifespan in developed countries has increased into middle adulthood. CF is a relatively common disorder that occurs in approximately 1 in 2000 Caucasians. A child born to two CF carriers would have a 25 percent chance of inheriting the disease. This is the same 3:1 dominant:recessive ratio that Mendel observed in his pea plants would apply here. The pattern is shown in **Figure 28.27**, using a diagram that tracks the likely incidence of an autosomal recessive disorder on the basis of parental genotypes.

On the other hand, a child born to a CF carrier and someone with two unaffected alleles would have a 0 percent probability of inheriting CF, but would have a 50 percent chance of being a carrier. Other examples of autosome recessive genetic illnesses include the blood disorder sickle-cell anemia, the fatal neurological disorder Tay–Sachs disease, and the metabolic disorder phenylketonuria.

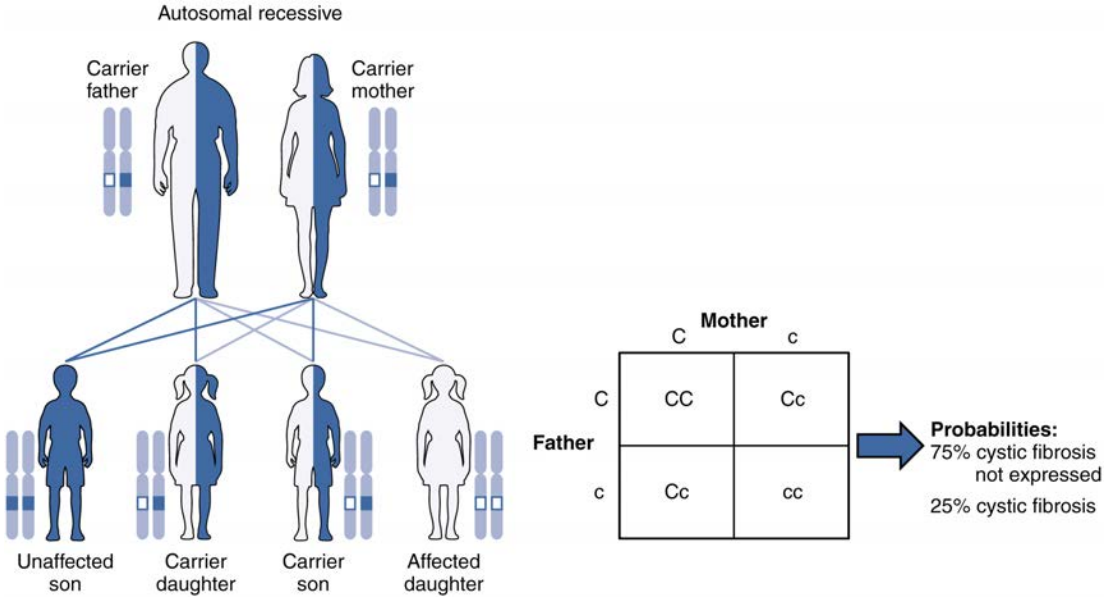



**Figure 28.27 Autosomal Recessive Inheritance** The inheritance pattern of an autosomal recessive disorder with two carrier parents reflects a 3:1 probability of expression among offspring. (credit: U.S. National Library of Medicine)

## X-linked Dominant or Recessive Inheritance

An **X-linked** transmission pattern involves genes located on the X chromosome of the 23rd pair (Figure 28.28). Recall that a male has one X and one Y chromosome. When a father transmits a Y chromosome, the child is male, and when he transmits an X chromosome, the child is female. A mother can transmit only an X chromosome, as both her sex chromosomes are X chromosomes.

When an abnormal allele for a gene that occurs on the X chromosome is dominant over the normal allele, the pattern is described as **X-linked dominant**. This is the case with vitamin D–resistant rickets: an affected father would pass the disease gene to all of his daughters, but none of his sons, because he donates only the Y chromosome to his sons (see Figure 28.28**a**). If it is the mother who is affected, all of her children—male or female—would have a 50 percent chance of inheriting the disorder because she can only pass an X chromosome on to her children (see Figure 28.28**b**). For an affected female, the inheritance pattern would be identical to that of an autosomal dominant inheritance pattern in which one parent is heterozygous and the other is homozygous for the normal gene.

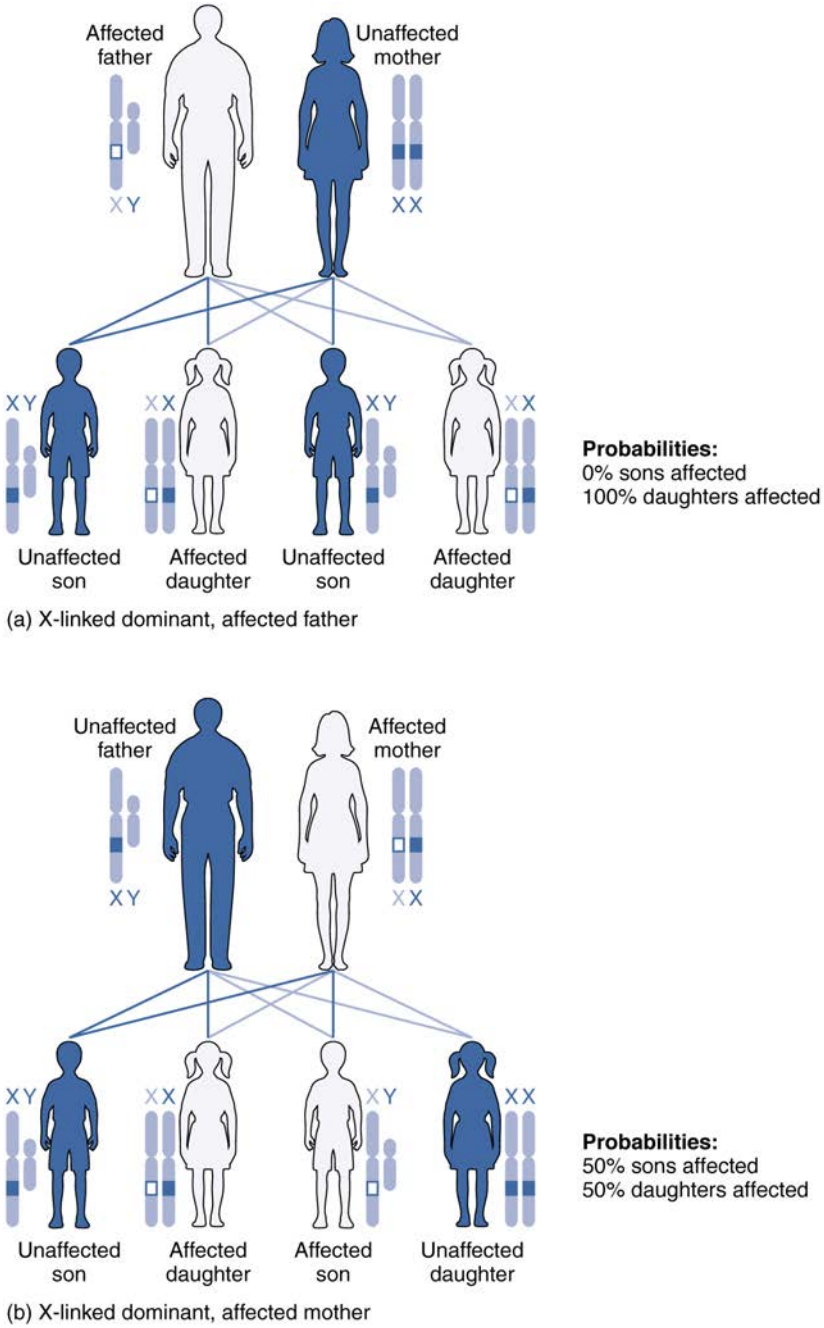



**Figure 28.28 X-Linked Patterns of Inheritance** A chart of X-linked dominant inheritance patterns differs depending on whether (a) the father or (b) the mother is affected with the disease. (credit: U.S. National Library of Medicine)

**X-linked recessive** inheritance is much more common because females can be carriers of the disease yet still have a normal phenotype. Diseases transmitted by X-linked recessive inheritance include color blindness, the blood-clotting

disorder hemophilia, and some forms of muscular dystrophy. For an example of X-linked recessive inheritance, consider parents in which the mother is an unaffected carrier and the father is normal. None of the daughters would have the disease because they receive a normal gene from their father. However, they have a 50 percent chance of receiving the disease gene from their mother and becoming a carrier. In contrast, 50 percent of the sons would be affected (**Figure 28.29**).

With X-linked recessive diseases, males either have the disease or are genotypically normal—they cannot be carriers. Females, however, can be genotypically normal, a carrier who is phenotypically normal, or affected with the disease. A daughter can inherit the gene for an X-linked recessive illness when her mother is a carrier or affected, or her father is affected. The daughter will be affected by the disease only if she inherits an X-linked recessive gene from both parents. As you can imagine, X-linked recessive disorders affect many more males than females. For example, color blindness affects at least 1 in 20 males, but only about 1 in 400 females.

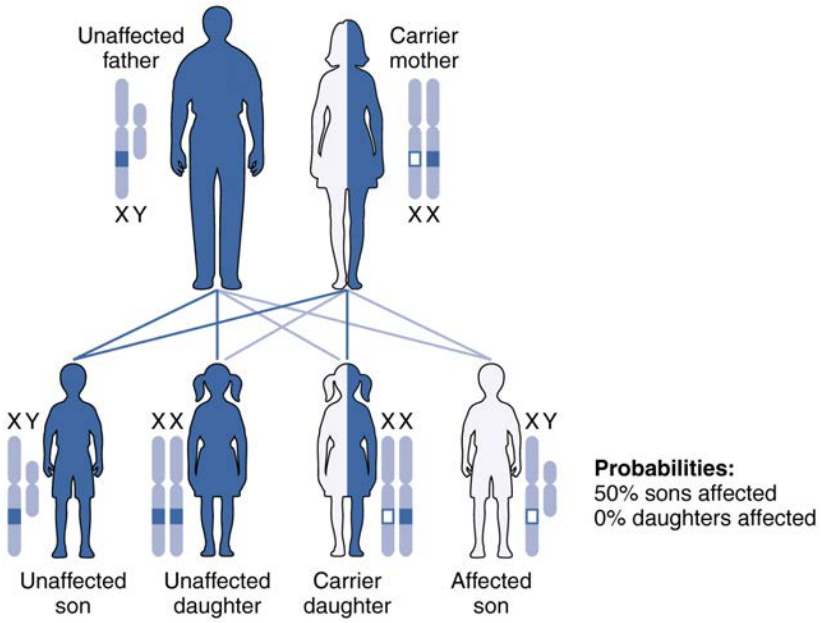



**Figure 28.29 X-Linked Recessive Inheritance** Given two parents in which the father is normal and the mother is a carrier of an X-linked recessive disorder, a son would have a 50 percent probability of being affected with the disorder, whereas daughters would either be carriers or entirely unaffected. (credit: U.S. National Library of Medicine)

## Other Inheritance Patterns: Incomplete Dominance, Codominance, and Lethal Alleles

Not all genetic disorders are inherited in a dominant–recessive pattern. In **incomplete dominance**, the offspring express a heterozygous phenotype that is intermediate between one parent's homozygous dominant trait and the other parent's homozygous recessive trait. An example of this can be seen in snapdragons when red-flowered plants and white-flowered plants are crossed to produce pink-flowered plants. In humans, incomplete dominance occurs with one of the genes for hair texture. When one parent passes a curly hair allele (the incompletely dominant allele) and the other parent passes a straight-hair allele, the effect on the offspring will be intermediate, resulting in hair that is wavy.

**Codominance** is characterized by the equal, distinct, and simultaneous expression of both parents' different alleles. This pattern differs from the intermediate, blended features seen in incomplete dominance. A classic example of codominance in humans is ABO blood type. People are blood type A if they have an allele for an enzyme that facilitates the production of surface antigen A on their erythrocytes. This allele is designated $I^A$. In the same manner, people are blood type B if they express an enzyme for the production of surface antigen B. People who have alleles for both enzymes ($I^A$ and $I^B$) produce both surface antigens A and B. As a result, they are blood type AB. Because the effect of both alleles (or enzymes) is observed, we say that the $I^A$ and $I^B$ alleles are codominant. There is also a third allele that determines blood type. This allele ($i$) produces a nonfunctional enzyme. People who have two $i$ alleles do not produce either A or B surface antigens: they have type O blood. If a person has $I^A$ and $i$ alleles, the person will have blood type A. Notice that it does not make any difference whether a person has two $I^A$ alleles or one $I^A$ and one $i$ allele. In both cases, the person is blood type A. Because $I^A$ masks $i$, we say that $I^A$ is dominant to $i$. **Table 28.4** summarizes the expression of blood type.

**Expression of Blood Types**

| Blood type | Genotype | Pattern of inheritance |
|---|---|---|
| A | $I^A I^A$ or $I^A i$ | $I^A$ is dominant to $i$ |
| B | $I^B I^B$ or $I^B i$ | $I^B$ is dominant to $i$ |
| AB | $I^A I^B$ | $I^A$ is co-dominant to $I^B$ |
| O | $ii$ | Two recessive alleles |

Table 28.4

Certain combinations of alleles can be lethal, meaning they prevent the individual from developing in utero, or cause a shortened life span. In **recessive lethal** inheritance patterns, a child who is born to two heterozygous (carrier) parents and who inherited the faulty allele from both would not survive. An example of this is Tay–Sachs, a fatal disorder of the nervous system. In this disorder, parents with one copy of the allele for the disorder are carriers. If they both transmit their abnormal allele, their offspring will develop the disease and will die in childhood, usually before age 5.

**Dominant lethal** inheritance patterns are much more rare because neither heterozygotes nor homozygotes survive. Of course, dominant lethal alleles that arise naturally through mutation and cause miscarriages or stillbirths are never transmitted to subsequent generations. However, some dominant lethal alleles, such as the allele for Huntington's disease, cause a shortened life span but may not be identified until after the person reaches reproductive age and has children. Huntington's disease causes irreversible nerve cell degeneration and death in 100 percent of affected individuals, but it may not be expressed until the individual reaches middle age. In this way, dominant lethal alleles can be maintained in the human population. Individuals with a family history of Huntington's disease are typically offered genetic counseling, which can help them decide whether or not they wish to be tested for the faulty gene.

## Mutations

A **mutation** is a change in the sequence of DNA nucleotides that may or may not affect a person's phenotype. Mutations can arise spontaneously from errors during DNA replication, or they can result from environmental insults such as radiation, certain viruses, or exposure to tobacco smoke or other toxic chemicals. Because genes encode for the assembly of proteins, a mutation in the nucleotide sequence of a gene can change amino acid sequence and, consequently, a protein's structure and function. Spontaneous mutations occurring during meiosis are thought to account for many spontaneous abortions (miscarriages).

## Chromosomal Disorders

Sometimes a genetic disease is not caused by a mutation in a gene, but by the presence of an incorrect number of chromosomes. For example, Down syndrome is caused by having three copies of chromosome 21. This is known as trisomy 21. The most common cause of trisomy 21 is chromosomal nondisjunction during meiosis. The frequency of nondisjunction events appears to increase with age, so the frequency of bearing a child with Down syndrome increases in women over 36. The age of the father matters less because nondisjunction is much less likely to occur in a sperm than in an egg.

Whereas Down syndrome is caused by having three copies of a chromosome, Turner syndrome is caused by having just one copy of the X chromosome. This is known as monosomy. The affected child is always female. Women with Turner syndrome are sterile because their sexual organs do not mature.

## Career CONNECTION

### Genetic Counselor

Given the intricate orchestration of gene expression, cell migration, and cell differentiation during prenatal development, it is amazing that the vast majority of newborns are healthy and free of major birth defects. When a woman over 35 is pregnant or intends to become pregnant, or her partner is over 55, or if there is a family history of a genetic disorder, she and her partner may want to speak to a genetic counselor to discuss the likelihood that their child may be affected by a genetic or chromosomal disorder. A genetic counselor can interpret a couple's family history and estimate the risks to their future offspring.

For many genetic diseases, a DNA test can determine whether a person is a carrier. For instance, carrier status for Fragile X, an X-linked disorder associated with mental retardation, or for cystic fibrosis can be determined with a simple blood draw to obtain DNA for testing. A genetic counselor can educate a couple about the implications of such a test and help them decide whether to undergo testing. For chromosomal disorders, the available testing options include a blood test, amniocentesis (in which amniotic fluid is tested), and chorionic villus sampling (in which tissue from the placenta is tested). Each of these has advantages and drawbacks. A genetic counselor can also help a couple cope with the news that either one or both partners is a carrier of a genetic illness, or that their unborn child has been diagnosed with a chromosomal disorder or other birth defect.

To become a genetic counselor, one needs to complete a 4-year undergraduate program and then obtain a Master of Science in Genetic Counseling from an accredited university. Board certification is attained after passing examinations by the American Board of Genetic Counseling. Genetic counselors are essential professionals in many branches of medicine, but there is a particular demand for preconception and prenatal genetic counselors.

## Interactive LINK

Visit the National Society of Genetic Counselors **website (http://openstaxcollege.org/l/gencounselor1)** for more information about genetic counselors.

## Interactive LINK

Visit the American Board of Genetic Counselors, Inc., **website (http://openstaxcollege.org/l/gencounselor2)** for more information about genetic counselors.

## KEY TERMS

**acrosomal reaction** release of digestive enzymes by sperm that enables them to burrow through the corona radiata and penetrate the zona pellucida of an oocyte prior to fertilization

**acrosome** cap-like vesicle located at the anterior-most region of a sperm that is rich with lysosomal enzymes capable of digesting the protective layers surrounding the oocyte

**afterbirth** third stage of childbirth in which the placenta and associated fetal membranes are expelled

**allantois** finger-like outpocketing of yolk sac forms the primitive excretory duct of the embryo; precursor to the urinary bladder

**allele** alternative forms of a gene that occupy a specific locus on a specific gene

**amnion** transparent membranous sac that encloses the developing fetus and fills with amniotic fluid

**amniotic cavity** cavity that opens up between the inner cell mass and the trophoblast; develops into amnion

**autosomal chromosome** in humans, the 22 pairs of chromosomes that are not the sex chromosomes (XX or XY)

**autosomal dominant** pattern of dominant inheritance that corresponds to a gene on one of the 22 autosomal chromosomes

**autosomal recessive** pattern of recessive inheritance that corresponds to a gene on one of the 22 autosomal chromosomes

**Braxton Hicks contractions** weak and irregular peristaltic contractions that can occur in the second and third trimesters; they do not indicate that childbirth is imminent

**blastocoel** fluid-filled cavity of the blastocyst

**blastocyst** term for the conceptus at the developmental stage that consists of about 100 cells shaped into an inner cell mass that is fated to become the embryo and an outer trophoblast that is fated to become the associated fetal membranes and placenta

**blastomere** daughter cell of a cleavage

**brown adipose tissue** highly vascularized fat tissue that is packed with mitochondria; these properties confer the ability to oxidize fatty acids to generate heat

**capacitation** process that occurs in the female reproductive tract in which sperm are prepared for fertilization; leads to increased motility and changes in their outer membrane that improve their ability to release enzymes capable of digesting an oocyte's outer layers

**carrier** heterozygous individual who does not display symptoms of a recessive genetic disorder but can transmit the disorder to his or her offspring

**chorion** membrane that develops from the syncytiotrophoblast, cytotrophoblast, and mesoderm; surrounds the embryo and forms the fetal portion of the placenta through the chorionic villi

**chorionic membrane** precursor to the chorion; forms from extra-embryonic mesoderm cells

**chorionic villi** projections of the chorionic membrane that burrow into the endometrium and develop into the placenta

**cleavage** form of mitotic cell division in which the cell divides but the total volume remains unchanged; this process serves to produce smaller and smaller cells

**codominance** pattern of inheritance that corresponds to the equal, distinct, and simultaneous expression of two different alleles

**colostrum** thick, yellowish substance secreted from a mother's breasts in the first postpartum days; rich in immunoglobulins

**conceptus** pre-implantation stage of a fertilized egg and its associated membranes

**corona radiata** in an oocyte, a layer of granulosa cells that surrounds the oocyte and that must be penetrated by sperm before fertilization can occur

**cortical reaction** following fertilization, the release of cortical granules from the oocyte's plasma membrane into the zona pellucida creating a fertilization membrane that prevents any further attachment or penetration of sperm; part of the slow block to polyspermy

**dilation** first stage of childbirth, involving an increase in cervical diameter

**dominant lethal** inheritance pattern in which individuals with one or two copies of a lethal allele do not survive in utero or have a shortened life span

**dominant** describes a trait that is expressed both in homozygous and heterozygous form

**ductus arteriosus** shunt in the pulmonary trunk that diverts oxygenated blood back to the aorta

**ductus venosus** shunt that causes oxygenated blood to bypass the fetal liver on its way to the inferior vena cava

**ectoderm** primary germ layer that develops into the central and peripheral nervous systems, sensory organs, epidermis, hair, and nails

**ectopic pregnancy** implantation of an embryo outside of the uterus

**embryo** developing human during weeks 3–8

**embryonic folding** process by which an embryo develops from a flat disc of cells to a three-dimensional shape resembling a cylinder

**endoderm** primary germ layer that goes on to form the gastrointestinal tract, liver, pancreas, and lungs

**epiblast** upper layer of cells of the embryonic disc that forms from the inner cell mass; gives rise to all three germ layers

**episiotomy** incision made in the posterior vaginal wall and perineum that facilitates vaginal birth

**expulsion** second stage of childbirth, during which the mother bears down with contractions; this stage ends in birth

**fertilization membrane** impenetrable barrier that coats a nascent zygote; part of the slow block to polyspermy

**fertilization** unification of genetic material from male and female haploid gametes

**fetus** developing human during the time from the end of the embryonic period (week 9) to birth

**foramen ovale** shunt that directly connects the right and left atria and helps divert oxygenated blood from the fetal pulmonary circuit

**foremilk** watery, translucent breast milk that is secreted first during a feeding and is rich in lactose and protein; quenches the infant's thirst

**gastrulation** process of cell migration and differentiation into three primary germ layers following cleavage and implantation

**genotype** complete genetic makeup of an individual

**gestation** in human development, the period required for embryonic and fetal development in utero; pregnancy

**heterozygous** having two different alleles for a given gene

**hindmilk** opaque, creamy breast milk delivered toward the end of a feeding; rich in fat; satisfies the infant's appetite

**homozygous** having two identical alleles for a given gene

**human chorionic gonadotropin (hCG)** hormone that directs the corpus luteum to survive, enlarge, and continue producing progesterone and estrogen to suppress menses and secure an environment suitable for the developing embryo

**hypoblast** lower layer of cells of the embryonic disc that extend into the blastocoel to form the yolk sac

**implantation** process by which a blastocyst embeds itself in the uterine endometrium

**incomplete dominance** pattern of inheritance in which a heterozygous genotype expresses a phenotype intermediate between dominant and recessive phenotypes

**inner cell mass** cluster of cells within the blastocyst that is fated to become the embryo

**involution** postpartum shrinkage of the uterus back to its pre-pregnancy volume

**karyotype** systematic arrangement of images of chromosomes into homologous pairs

**lactation** process by which milk is synthesized and secreted from the mammary glands of the postpartum female breast in response to sucking at the nipple

**lanugo** silk-like hairs that coat the fetus; shed later in fetal development

**let-down reflex** release of milk from the alveoli triggered by infant suckling

**lightening** descent of the fetus lower into the pelvis in late pregnancy; also called “dropping”

**lochia** postpartum vaginal discharge that begins as blood and ends as a whitish discharge; the end of lochia signals that the site of placental attachment has healed

**meconium** fetal wastes consisting of ingested amniotic fluid, cellular debris, mucus, and bile

**mesoderm** primary germ layer that becomes the skeleton, muscles, connective tissue, heart, blood vessels, and kidneys

**morula** tightly packed sphere of blastomeres that has reached the uterus but has not yet implanted itself

**mutation** change in the nucleotide sequence of DNA

**neural fold** elevated edge of the neural groove

**neural plate** thickened layer of neuroepithelium that runs longitudinally along the dorsal surface of an embryo and gives rise to nervous system tissue

**neural tube** precursor to structures of the central nervous system, formed by the invagination and separation of neuroepithelium

**neurulation** embryonic process that establishes the central nervous system

**nonshivering thermogenesis** process of breaking down brown adipose tissue to produce heat in the absence of a shivering response

**notochord** rod-shaped, mesoderm-derived structure that provides support for growing fetus

**organogenesis** development of the rudimentary structures of all of an embryo’s organs from the germ layers

**Punnett square** grid used to display all possible combinations of alleles transmitted by parents to offspring and predict the mathematical probability of offspring inheriting a given genotype

**parturition** childbirth

**phenotype** physical or biochemical manifestation of the genotype; expression of the alleles

**placenta previa** low placement of fetus within uterus causes placenta to partially or completely cover the opening of the cervix as it grows

**placenta** organ that forms during pregnancy to nourish the developing fetus; also regulates waste and gas exchange between mother and fetus

**placentation** formation of the placenta; complete by weeks 14–16 of pregnancy

**polyspermy** penetration of an oocyte by more than one sperm

**primitive streak** indentation along the dorsal surface of the epiblast through which cells migrate to form the endoderm and mesoderm during gastrulation

**prolactin** pituitary hormone that establishes and maintains the supply of breast milk; also important for the mobilization of maternal micronutrients for breast milk

**quickening** fetal movements that are strong enough to be felt by the mother

**recessive lethal** inheritance pattern in which individuals with two copies of a lethal allele do not survive in utero or have a shortened life span

**recessive** describes a trait that is only expressed in homozygous form and is masked in heterozygous form

**sex chromosomes** pair of chromosomes involved in sex determination; in males, the XY chromosomes; in females, the XX chromosomes

**shunt** circulatory shortcut that diverts the flow of blood from one region to another

**somite** one of the paired, repeating blocks of tissue located on either side of the notochord in the early embryo

**syncytiotrophoblast** superficial cells of the trophoblast that fuse to form a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall

**trait** variation of an expressed characteristic

**trimester** division of the duration of a pregnancy into three 3-month terms

**trophoblast** fluid-filled shell of squamous cells destined to become the chorionic villi, placenta, and associated fetal membranes

**true labor** regular contractions that immediately precede childbirth; they do not abate with hydration or rest, and they become more frequent and powerful with time

**umbilical cord** connection between the developing conceptus and the placenta; carries deoxygenated blood and wastes from the fetus and returns nutrients and oxygen from the mother

**vernix caseosa** waxy, cheese-like substance that protects the delicate fetal skin until birth

**X-linked dominant** pattern of dominant inheritance that corresponds to a gene on the X chromosome of the 23rd pair

**X-linked recessive** pattern of recessive inheritance that corresponds to a gene on the X chromosome of the 23rd pair

**X-linked** pattern of inheritance in which an allele is carried on the X chromosome of the 23rd pair

**yolk sac** membrane associated with primitive circulation to the developing embryo; source of the first blood cells and germ cells and contributes to the umbilical cord structure

**zona pellucida** thick, gel-like glycoprotein membrane that coats the oocyte and must be penetrated by sperm before fertilization can occur

**zygote** fertilized egg; a diploid cell resulting from the fertilization of haploid gametes from the male and female lines

## CHAPTER REVIEW

### 28.1 Fertilization

Hundreds of millions of sperm deposited in the vagina travel toward the oocyte, but only a few hundred actually reach it. The number of sperm that reach the oocyte is greatly reduced because of conditions within the female reproductive tract. Many sperm are overcome by the acidity of the vagina, others are blocked by mucus in the cervix, whereas others are attacked by phagocytic leukocytes in the uterus. Those sperm that do survive undergo a change in response to those conditions. They go through the process of capacitation, which improves their motility and alters the membrane surrounding the acrosome, the cap-like structure in the head of a sperm that contains the digestive enzymes needed for it to attach to and penetrate the oocyte.

The oocyte that is released by ovulation is protected by a thick outer layer of granulosa cells known as the corona radiata and by the zona pellucida, a thick glycoprotein membrane that lies just outside the oocyte's plasma membrane. When capacitated sperm make contact with the oocyte, they release the digestive enzymes in the acrosome (the acrosomal reaction) and are thus able to attach to the oocyte and burrow through to the oocyte's zona pellucida. One of the sperm will then break through to the oocyte's plasma membrane and release its haploid nucleus into the oocyte. The oocyte's

membrane structure changes in response (cortical reaction), preventing any further penetration by another sperm and forming a fertilization membrane. Fertilization is complete upon unification of the haploid nuclei of the two gametes, producing a diploid zygote.

## 28.2 Embryonic Development

As the zygote travels toward the uterus, it undergoes numerous cleavages in which the number of cells doubles (blastomeres). Upon reaching the uterus, the conceptus has become a tightly packed sphere of cells called the morula, which then forms into a blastocyst consisting of an inner cell mass within a fluid-filled cavity surrounded by trophoblasts. The blastocyst implants in the uterine wall, the trophoblasts fuse to form a syncytiotrophoblast, and the conceptus is enveloped by the endometrium. Four embryonic membranes form to support the growing embryo: the amnion, the yolk sac, the allantois, and the chorion. The chorionic villi of the chorion extend into the endometrium to form the fetal portion of the placenta. The placenta supplies the growing embryo with oxygen and nutrients; it also removes carbon dioxide and other metabolic wastes.

Following implantation, embryonic cells undergo gastrulation, in which they differentiate and separate into an embryonic disc and establish three primary germ layers (the endoderm, mesoderm, and ectoderm). Through the process of embryonic folding, the fetus begins to take shape. Neurulation starts the process of the development of structures of the central nervous system and organogenesis establishes the basic plan for all organ systems.

## 28.3 Fetal Development

The fetal period lasts from the ninth week of development until birth. During this period, male and female gonads differentiate. The fetal circulatory system becomes much more specialized and efficient than its embryonic counterpart. It includes three shunts—the ductus venosus, the foramen ovale, and the ductus arteriosus—that enable it to bypass the semifunctional liver and pulmonary circuit until after childbirth. The brain continues to grow and its structures differentiate. Facial features develop, the body elongates, and the skeleton ossifies. In the womb, the developing fetus moves, blinks, practices sucking, and circulates amniotic fluid. The fetus grows from an embryo measuring approximately 3.3 cm (1.3 in) and weighing 7 g (0.25 oz) to an infant measuring approximately 51 cm (20 in) and weighing an average of approximately 3.4 kg (7.5 lbs). Embryonic organ structures that were primitive and nonfunctional develop to the point that the newborn can survive in the outside world.

## 28.4 Maternal Changes During Pregnancy, Labor, and Birth

Hormones (especially estrogens, progesterone, and hCG) secreted by the corpus luteum and later by the placenta are responsible for most of the changes experienced during pregnancy. Estrogen maintains the pregnancy, promotes fetal viability, and stimulates tissue growth in the mother and developing fetus. Progesterone prevents new ovarian follicles from developing and suppresses uterine contractility.

Pregnancy weight gain primarily occurs in the breasts and abdominal region. Nausea, heartburn, and frequent urination are common during pregnancy. Maternal blood volume increases by 30 percent during pregnancy and respiratory minute volume increases by 50 percent. The skin may develop stretch marks and melanin production may increase.

Toward the late stages of pregnancy, a drop in progesterone and stretching forces from the fetus lead to increasing uterine irritability and prompt labor. Contractions serve to dilate the cervix and expel the newborn. Delivery of the placenta and associated fetal membranes follows.

## 28.5 Adjustments of the Infant at Birth and Postnatal Stages

The first breath a newborn takes at birth inflates the lungs and dramatically alters the circulatory system, closing the three shunts that directed oxygenated blood away from the lungs and liver during fetal life. Clamping and cutting the umbilical cord collapses the three umbilical blood vessels. The proximal umbilical arteries remain a part of the circulatory system, whereas the distal umbilical arteries and the umbilical vein become fibrotic. The newborn keeps warm by breaking down brown adipose tissue in the process of nonshivering thermogenesis. The first consumption of breast milk or formula floods the newborn’s sterile gastrointestinal tract with beneficial bacteria that eventually establish themselves as the bacterial flora, which aid in digestion.

## 28.6 Lactation

The lactating mother supplies all the hydration and nutrients that a growing infant needs for the first 4–6 months of life. During pregnancy, the body prepares for lactation by stimulating the growth and development of branching lactiferous ducts and alveoli lined with milk-secreting lactocytes, and by creating colostrum. These functions are attributable to the actions of several hormones, including prolactin. Following childbirth, suckling triggers oxytocin release, which stimulates myoepithelial cells to squeeze milk from alveoli. Breast milk then drains toward the nipple pores to be consumed by the infant. Colostrum, the milk produced in the first postpartum days, provides immunoglobulins that increase the newborn’s immune defenses. Colostrum, transitional milk, and mature breast milk are ideally suited to each stage of the newborn’s development, and breastfeeding helps the newborn’s digestive system expel meconium and clear bilirubin. Mature milk

changes from the beginning to the end of a feeding. Foremilk quenches the infant's thirst, whereas hindmilk satisfies the infant's appetite.

### 28.7 Patterns of Inheritance

There are two aspects to a person's genetic makeup. Their genotype refers to the genetic makeup of the chromosomes found in all their cells and the alleles that are passed down from their parents. Their phenotype is the expression of that genotype, based on the interaction of the paired alleles, as well as how environmental conditions affect that expression.

Working with pea plants, Mendel discovered that the factors that account for different traits in parents are discretely transmitted to offspring in pairs, one from each parent. He articulated the principles of random segregation and independent assortment to account for the inheritance patterns he observed. Mendel's factors are genes, with differing variants being referred to as alleles and those alleles being dominant or recessive in expression. Each parent passes one allele for every gene on to offspring, and offspring are equally likely to inherit any combination of allele pairs. When Mendel crossed heterozygous individuals, he repeatedly found a 3:1 dominant–recessive ratio. He correctly postulated that the expression of the recessive trait was masked in heterozygotes but would resurface in their offspring in a predictable manner.

Human genetics focuses on identifying different alleles and understanding how they express themselves. Medical researchers are especially interested in the identification of inheritance patterns for genetic disorders, which provides the means to estimate the risk that a given couple's offspring will inherit a genetic disease or disorder. Patterns of inheritance in humans include autosomal dominance and recessiveness, X-linked dominance and recessiveness, incomplete dominance, codominance, and lethality. A change in the nucleotide sequence of DNA, which may or may not manifest in a phenotype, is called a mutation.

## INTERACTIVE LINK QUESTIONS

**1.** View this time-lapse **movie (http://openstaxcollege.org/l/conceptus)** of a conceptus starting at day 3. What is the first structure you see? At what point in the movie does the blastocoel first appear? What event occurs at the end of the movie?

**2.** Use this interactive **tool (http://openstaxcollege.org/l/embryogenesis)** to view the process of embryogenesis from the perspective of the conceptus (left panel), as well as fetal development viewed from a maternal cross-section (right panel). Can you identify when neurulation occurs in the embryo?

**3.** Visit this **site (http://openstaxcollege.org/l/pregstages)** for a summary of the stages of pregnancy, as experienced by the mother, and view the stages of development of the fetus throughout gestation. At what point in fetal development can a regular heartbeat be detected?

## REVIEW QUESTIONS

**4.** Sperm and ova are similar in terms of _____.

a. size
b. quantity produced per year
c. chromosome number
d. flagellar motility

**5.** Although the male ejaculate contains hundreds of millions of sperm, _____.

a. most do not reach the oocyte
b. most are destroyed by the alkaline environment of the uterus
c. it takes millions to penetrate the outer layers of the oocyte
d. most are destroyed by capacitation

**6.** As sperm first reach the oocyte, they will contact the _____.

a. acrosome
b. corona radiata
c. sperm-binding receptors
d. zona pellucida

**7.** Fusion of pronuclei occurs during _____.

a. spermatogenesis
b. ovulation
c. fertilization
d. capacitation

**8.** Sperm must first complete _____ to enable the fertilization of an oocyte.

a. capacitation
b. the acrosomal reaction
c. the cortical reaction
d. the fast block

**9.** Cleavage produces daughter cells called _____.

a. trophoblasts
b. blastocysts
c. morulae
d. blastomeres

**10.** The conceptus, upon reaching the uterus, first _____.

a. implants
b. divides
c. disintegrates
d. hatches

**11.** The inner cell mass of the blastocyst is destined to become the _____.

a. embryo
b. trophoblast
c. chorionic villi
d. placenta

**12.** Which primary germ layer gave rise to the cells that eventually became the central nervous system?
- a. endoderm
- b. ectoderm
- c. acrosome
- d. mesoderm

**13.** What would happen if the trophoblast did not secrete hCG upon implantation of the blastocyst?
- a. The cells would not continue to divide.
- b. The corpus luteum would continue to produce progesterone and estrogen.
- c. Menses would flush the blastocyst out of the uterus.
- d. The uterine mucosa would not envelop the blastocyst.

**14.** During what process does the amnion envelop the embryo?
- a. embryonic folding
- b. gastrulation
- c. implantation
- d. organogenesis

**15.** The placenta is formed from _____.
- a. the embryo's mesenchymal cells
- b. the mother's endometrium only
- c. the mother's endometrium and the embryo's chorionic membrane
- d. the mother's endometrium and the embryo's umbilical cord

**16.** The foramen ovale causes the fetal circulatory system to bypass the _____.
- a. liver
- b. lungs
- c. kidneys
- d. gonads

**17.** What happens to the urine excreted by the fetus when the kidneys begin to function?
- a. The umbilical cord carries it to the placenta for removal.
- b. The endometrium absorbs it.
- c. It adds to the amniotic fluid.
- d. It is turned into meconium.

**18.** During weeks 9–12 of fetal development, _____.
- a. bone marrow begins to assume erythrocyte production
- b. meconium begins to accumulate in the intestines
- c. surfactant production begins in the fetal lungs
- d. the spinal cord begins to be myelinated

**19.** Progesterone secreted by the placenta suppresses _____ to prevent maturation of ovarian follicles.
- a. LH and estrogen
- b. hCG and FSH
- c. FSH and LH
- d. estrogen and hCG

**20.** Which of the following is a possible culprit of "morning sickness"?
- a. increased minute respiration
- b. decreased intestinal peristalsis
- c. decreased aldosterone secretion
- d. increased blood volume

**21.** How does the decrease in progesterone at the last weeks of pregnancy help to bring on labor?
- a. stimulating FSH production
- b. decreasing the levels of estrogens
- c. dilating the cervix
- d. decreasing the inhibition of uterine contractility

**22.** Which of these fetal presentations is the easiest for vaginal birth?
- a. complete breech
- b. vertex occiput anterior
- c. frank breech
- d. vertex occiput posterior

**23.** Which of these shunts exists between the right and left atria?
- a. foramen ovale
- b. ductus venosus
- c. ductus arteriosis
- d. foramen venosus

**24.** Why is brown fat important?
- a. It is the newborn's primary source of insulation.
- b. It can be broken down to generate heat for thermoregulation.
- c. It can be broken down for energy between feedings.
- d. It can be converted to white fat.

**25.** Constriction of umbilical blood vessels during vaginal birth _____.
- a. causes respiratory alkalosis
- b. inhibits the respiratory center in the brain
- c. elevates carbon dioxide levels in the blood
- d. both a and b

**26.** Alveoli are connected to the lactiferous sinuses by _____.
- a. lactocytes
- b. lactiferous ducts
- c. nipple pores
- d. lobules

**27.** How is colostrum most important to a newborn?
- a. It helps boost the newborn's immune system.
- b. It provides much needed fat.
- c. It satisfies the newborn's thirst.
- d. It satisfies the infant's appetite.

**28.** Mature breast milk _____.
- a. has more sodium than cow's milk
- b. has more calcium than cow's milk
- c. has more protein than cow's milk
- d. has more fat than cow's milk

**29.** Marfan syndrome is inherited in an autosomal dominant pattern. Which of the following is true?
- a. Female offspring are more likely to be carriers of the disease.
- b. Male offspring are more likely to inherit the disease.
- c. Male and female offspring have the same likelihood of inheriting the disease.

d. Female offspring are more likely to inherit the disease.

**30.** In addition to codominance, the ABO blood group antigens are also an example of _____.

a. incomplete dominance
b. X-linked recessive inheritance
c. multiple alleles
d. recessive lethal inheritance

**31.** Zoe has cystic fibrosis. Which of the following is the most likely explanation?

a. Zoe probably inherited one faulty allele from her father, who is a carrier, and one normal allele from her mother.
b. Zoe probably inherited one faulty allele from her mother, who must also have cystic fibrosis, and one normal allele from her father.
c. Zoe must have inherited faulty alleles from both parents, both of whom must also have cystic fibrosis.
d. Zoe must have inherited faulty alleles from both parents, both of whom are carriers.

## CRITICAL THINKING QUESTIONS

**32.** Darcy and Raul are having difficulty conceiving a child. Darcy ovulates every 28 days, and Raul's sperm count is normal. If we could observe Raul's sperm about an hour after ejaculation, however, we'd see that they appear to be moving only sluggishly. When Raul's sperm eventually encounter Darcy's oocyte, they appear to be incapable of generating an adequate acrosomal reaction. Which process has probably gone wrong?

**33.** Sherrise is a sexually active college student. On Saturday night, she has unprotected sex with her boyfriend. On Tuesday morning, she experiences the twinge of mid-cycle pain that she typically feels when she is ovulating. This makes Sherrise extremely anxious that she might soon learn she is pregnant. Is Sherrise's concern valid? Why or why not?

**34.** Approximately 3 weeks after her last menstrual period, a sexually active woman experiences a brief episode of abdominopelvic cramping and minor bleeding. What might be the explanation?

**35.** The Food and Nutrition Board of the Institute of Medicine recommends that all women who might become pregnant consume at least 400 µg/day of folate from supplements or fortified foods. Why?

**36.** What is the physiological benefit of incorporating shunts into the fetal circulatory system?

**37.** Why would a premature infant require supplemental oxygen?

**38.** Devin is 35 weeks pregnant with her first child when she arrives at the birthing unit reporting that she believes she is in labor. She states that she has been experiencing diffuse, mild contractions for the past few hours. Examination reveals, however, that the plug of mucus blocking her cervix is intact and her cervix has not yet begun to dilate. She is advised to return home. Why?

**39.** Janine is 41 weeks pregnant with her first child when she arrives at the birthing unit reporting that she believes she has been in labor "for days" but that "it's just not going anywhere." During the clinical exam, she experiences a few mild contractions, each lasting about 15–20 seconds; however, her cervix is found to be only 2 cm dilated, and the amniotic sac is intact. Janine is admitted to the birthing unit and an IV infusion of pitocin is started. Why?

**40.** Describe how the newborn's first breath alters the circulatory pattern.

**41.** Newborns are at much higher risk for dehydration than adults. Why?

**42.** Describe the transit of breast milk from lactocytes to nipple pores.

**43.** A woman who stopped breastfeeding suddenly is experiencing breast engorgement and leakage, just like she did in the first few weeks of breastfeeding. Why?

**44.** Explain why it was essential that Mendel perform his crosses using a large sample size?

**45.** How can a female carrier of an X-linked recessive disorder have a daughter who is affected?

# ANSWER KEY

## Chapter 1

**1** Fatty acid catabolism. **2** The kidneys. **3** X-rays. **4** The magnets induce tissue to emit radio signals that can show differences between different types of tissue. **5** PET scans can indicate how patients are responding to chemotherapy. **6** C **7** A **8** A **9** A **10** D **11** D **12** C **13** A **14** C **15** A **16** C **17** A **18** C **19** B **20** D **21** C **22** D **23** B **24** D **25** C **26** C **27** B **28** An understanding of anatomy and physiology is essential for any career in the health professions. It can also help you make choices that promote your health, respond appropriately to signs of illness, make sense of health-related news, and help you in your roles as a parent, spouse, partner, friend, colleague, and caregiver. **29** A student would more readily appreciate the structures revealed in the dissection. Even though the student has not yet studied the workings of the heart and blood vessels in her class, she has experienced her heart beating every moment of her life, has probably felt her pulse, and likely has at least a basic understanding of the role of the heart in pumping blood throughout her body. This understanding of the heart's function (physiology) would support her study of the heart's form (anatomy). **30** Chemical, cellular, tissue, organ, organ system, organism. **31** The female ovaries and the male testes are parts of the reproductive system. But they also secrete hormones, as does the endocrine system, therefore ovaries and testes function within both the endocrine and reproductive systems. **32** When you are sitting at a campfire, your sense of smell adapts to the smell of smoke. Only if that smell were to suddenly and dramatically intensify would you be likely to notice and respond. In contrast, the smell of even a trace of smoke would be new and highly unusual in your residence hall, and would be perceived as danger. **33** Growth can occur by increasing the number of existing cells, increasing the size of existing cells, or increasing the amount of non-cellular material around cells. **34** In a sealed bottle of sparkling water, carbon dioxide gas is kept dissolved in the water under a very high pressure. When you open the bottle, the pressure of the gas above the liquid changes from artificially high to normal atmospheric pressure. The dissolved carbon dioxide gas expands, and rises in bubbles to the surface. When a bottle of sparkling water is left open, it eventually goes flat because its gases continue to move out of solution until the pressure in the water is approximately equal to atmospheric pressure. **35** The primary way that the body responds to high environmental heat is by sweating; however, sweating requires water, which comes from body fluids, including blood plasma. If Josh becomes dehydrated, he will be unable to sweat adequately to cool his body, and he will be at risk for heat stroke as his blood pressure drops too much from the loss of water from the blood plasma. **36** The four components of a negative feedback loop are: stimulus, sensor, control center, and effector. If too great a quantity of the chemical were excreted, sensors would activate a control center, which would in turn activate an effector. In this case, the effector (the secreting cells) would be adjusted downward. **37** Any prolonged exposure to extreme cold would activate the brain's heat-gain center. This would reduce blood flow to your skin, and shunt blood returning from your limbs away from the digits and into a network of deep veins. Your brain's heat-gain center would also increase your muscle contraction, causing you to shiver. This increases the energy consumption of skeletal muscle and generates more heat. Your body would also produce thyroid hormone and epinephrine, chemicals that promote increased metabolism and heat production. **38** If the body were supine or prone, the MRI scanner would move from top to bottom to produce frontal sections, which would divide the body into anterior and posterior portions, as in "cutting" a deck of cards. Again, if the body were supine or prone, to produce sagittal sections, the scanner would move from left to right or from right to left to divide the body lengthwise into left and right portions. **39** The bullet would enter the ventral, thoracic, and pleural cavities, and it would encounter the parietal layer of serous membrane first. **40** CT scanning subjects patients to much higher levels of radiation than X-rays, and should not be performed repeatedly. **41** Ultrasonography does not expose a mother or fetus to radiation, to radiopharmaceuticals, or to magnetic fields. At this time, there are no known medical risks of ultrasonography.

## Chapter 2

**1** The mass number is the total number of protons and neutrons in the nucleus of an atom. **2** The plastic sheets jump to the nail (the conductor), because the conductor takes on electrons from the electroscope, reducing the repellant force of the two sheets. **3** The water hydrolyses, or breaks, the glycosidic bond, forming two monosaccharides. **4** D **5** B **6** A **7** C **8** B **9** C **10** C **11** A **12** B **13** A **14** A **15** B **16** C **17** D **18** A **19** D **20** B **21** A **22** D **23** C **24** B **25** C **26** A **27** C **28** B **29** A **30** D **31** D **32** B **33** These four elements—oxygen, carbon, hydrogen, and nitrogen—together make up more than 95 percent of the mass of the human body, and the body cannot make elements, so it is helpful to have them in consumables. **34** Oxygen has eight protons. In its most abundant stable form, it has eight neutrons, too, for a mass number of 16. In contrast, $^{17}O$ has nine neutrons, and $^{18}O$ has 10 neutrons. **35** Magnesium's 12 electrons are distributed as follows: two in the first shell, eight in the second shell, and two in its valence shell. According to the octet rule, magnesium is unstable (reactive) because its valence shell has just two electrons. It is therefore likely to participate in chemical reactions in which it donates two electrons. **36** A carbon atom has four electrons in its valence shell. According to the octet rule, it will readily participate in chemical reactions that result in its valence shell having eight electrons. Hydrogen, with one electron, will complete its valence shell with two. Electron sharing between an atom of carbon and four atoms of hydrogen meets the requirements of all atoms. The bonds are covalent because the electrons are shared: although hydrogen often participates in ionic bonds, carbon does not because it is highly unlikely to donate or accept four electrons. **37** Water is a polar molecule. It has a region of weakly positive charge and a region of weakly negative charge. These regions are attracted to ions as well as to other polar molecules. Oils are nonpolar, and are repelled by water. **38** Identical atoms have identical electronegativity and cannot form ionic bonds. Oxygen, for example, has six electrons in its valence shell. Neither donating nor accepting the valence shell electrons of the other will result in the oxygen atoms completing their valence shells. Two atoms of the same element always form covalent bonds. **39** It is not. An exchange reaction might be $AB + CD \rightarrow AC + BD$ or

$AB + CD \rightarrow AD + BC$. In all chemical reactions, including exchange reactions, the components of the reactants are identical to the components of the products. A component present among the reactants cannot disappear, nor can a component not present in the reactants suddenly appear in the products. **40** Recall that the greater the surface area of the reactants, the more quickly and easily they will interact. It takes energy to separate particles of a substance. Powder and liquid laundry detergents, with relatively more surface area per unit, can quickly dissolve into their reactive components when added to the water. **41** Lemon juice is one hundred times more acidic than orange juice. This means that lemon juice has a one hundred-fold greater concentration of hydrogen ions. **42** Lemon juice, like any acid, releases hydrogen ions in solution. As excessive $H^+$ enters the digestive tract and is absorbed into blood, Eli's blood pH falls below 7.35. Recall that bicarbonate is a buffer, a weak base that accepts hydrogen ions. By administering bicarbonate intravenously, the emergency department physician helps raise Eli's blood pH back toward neutral. **43** Maltose contains 12 atoms of carbon, but only 22 atoms of hydrogen and 11 atoms of oxygen, because a molecule of water is removed during its formation via dehydration synthesis. **44** All lipids are hydrophobic and unable to dissolve in the watery environment of blood. They are packaged into lipoproteins, whose outer protein envelope enables them to transport fats in the bloodstream.

## Chapter 3

**1** Higher temperatures speed up diffusion because molecules have more kinetic energy at higher temperatures. **2** Processing, packaging, and moving materials manufactured by the cell. **3** an enzyme **4** They separate and move and are free to join translation of other segments of mRNA. **5** the spindle **6** B **7** D **8** C **9** B **10** D **11** B **12** A **13** C **14** A **15** B **16** C **17** C **18** A **19** B **20** C **21** A **22** C **23** D **24** B **25** D **26** B **27** D **28** C **29** C **30** Only materials that are relatively small and nonpolar can easily diffuse through the lipid bilayer. Large particles cannot fit in between the individual phospholipids that are packed together, and polar molecules are repelled by the hydrophobic/nonpolar lipids that line the inside of the bilayer. **31** Receptor-mediated endocytosis is more selective because the substances that are brought into the cell are the specific ligands that could bind to the receptors being endocytosed. Phagocytosis or pinocytosis, on the other hand, have no such receptor-ligand specificity, and bring in whatever materials happen to be close to the membrane when it is enveloped. **32** These four phenomena are similar in the sense that they describe the movement of substances down a particular type of gradient. Osmosis and diffusion involve the movement of water and other substances down their concentration gradients, respectively. Filtration describes the movement of particles down a pressure gradient, and the movement of ions away from like charge describes their movement down their electrical gradient. **33** The structure of the Golgi apparatus is suited to its function because it is a series of flattened membranous discs; substances are modified and packaged in sequential steps as they travel from one disc to the next. The structure of Golgi apparatus also involves a receiving face and a sending face, which organize cellular products as they enter and leave the Golgi apparatus. The ER and the mitochondria both have structural specializations that increase their surface area. In the mitochondria, the inner membrane is extensively folded, which increases surface area for ATP production. Likewise, the ER is elaborately wound throughout the cell, increasing its surface area for functions like lipid synthesis, $Ca^{++}$ storage, and protein synthesis. **34** Peroxisomes and lysosomes are both cellular organelles bound by lipid bilayer membranes, and they both contain many enzymes. However, peroxisomes contain enzymes that detoxify substances by transferring hydrogen atoms and producing $H_2O_2$, whereas the enzymes in lysosomes function to break down and digest various unwanted materials. **35** DNA replication is said to be semiconservative because, after replication is complete, one of the two parent DNA strands makes up half of each new DNA molecule. The other half is a newly synthesized strand. Therefore, half ("semi") of each daughter DNA molecule is from the parent molecule and half is a new molecule. **36** During cell division, one cell divides to produce two new cells. In order for all of the cells in your body to maintain a full genome, each cell must replicate its DNA before it divides so that a full genome can be allotted to each of its offspring cells. If DNA replication did not take place fully, or at all, the offspring cells would be missing some or all of the genome. This could be disastrous if a cell was missing genes necessary for its function and health. **37** Transcription and DNA replication both involve the synthesis of nucleic acids. These processes share many common features—particularly, the similar processes of initiation, elongation, and termination. In both cases the DNA molecule must be untwisted and separated, and the coding (i.e., sense) strand will be used as a template. Also, polymerases serve to add nucleotides to the growing DNA or mRNA strand. Both processes are signaled to terminate when completed. **38** Transcription is really a "copy" process and translation is really an "interpretation" process, because transcription involves copying the DNA message into a very similar RNA message whereas translation involves converting the RNA message into the very different amino acid message. The two processes also differ in their location: transcription occurs in the nucleus and translation in the cytoplasm. The mechanisms by which the two processes are performed are also completely different: transcription utilizes polymerase enzymes to build mRNA whereas translation utilizes different kinds of RNA to build protein. **39** One or both of the new daughter cells would accidently receive duplicate chromosomes and/or would be missing certain chromosomes. **40** A cyclin is one of the primary classes of cell cycle control molecules, while a cyclin-dependent kinase (is one of a group of molecules that work together with cyclins to determine progression past cell checkpoints. By interacting with many additional molecules, these triggers push the cell cycle forward unless prevented from doing so by "stop" signals, if for some reason the cell is not ready. **41** Transcription factors bind to DNA and either promote or inhibit the transcription of a gene. If they promote the transcription of a particular gene, then that gene will be transcribed and the mRNA subsequently translated into protein. If gene transcription is inhibited, then there will be no way of synthesizing the gene's corresponding protein. **42** Embryonic stem cells derive from human embryos, which are destroyed to obtain the cells. The destruction of human embryos is an ethical problem. And, the DNA in an embryonic stem cell would differ from the DNA of the person being treated, which could result in immune problems or rejected of tissue.

## Chapter 4

**1** Most somatic stem cells give rise to only a few cell types. **2** The inside of the mouth, esophagus, vaginal canal, and anus. **3** Click at the bottom of the quiz for the answers. **4** Skeletal muscle cells are striated. **5** Dendrites, cell body, and the axon. **6** Approximately one month. **7** A mass of cancer cells that continue to grow and divide. **8** C **9** A **10** B **11** D **12** A **13** C **14** B **15** A **16** B **17** D **18** B **19** C **20** B **21** D **22** A **23** A **24** D **25** A **26** B **27** D **28** C **29** B **30** B **31** C **32** The four types of tissue in the body are epithelial, connective, muscle, and nervous. Epithelial tissue is made of layers of cells that cover the surfaces of the body that come into contact with the exterior world, line internal cavities, and form glands. Connective tissue binds the cells and organs of the body together and performs many functions, especially in the protection, support, and integration of the body. Muscle tissue, which responds to stimulation and contracts to provide movement, is divided into three major types: skeletal (voluntary) muscles, smooth muscles, and the cardiac muscle in the heart. Nervous tissue allows the body to receive signals and transmit information as electric impulses from one region of the body to another. **33** The zygote divides into many cells. As these cells become specialized, they lose their ability to differentiate into all tissues. At first they form the three primary germ layers. Following the cells of the ectodermal germ layer, they too become more restricted in what they can form. Ultimately, some of these ectodermal cells become further restricted and differentiate in to nerve cells. **34** Synovial membranes are a type of connective tissue membrane that supports mobility in joints. The membrane lines the joint cavity and contains fibroblasts that produce hyaluronan, which leads to the production of synovial fluid, a natural lubricant that enables the bones of a joint to move freely against one another. **35** Columnar epithelia, which form the lining of the digestive tract, can be either simple or stratified. The cells are long and narrow. The nucleus is elongated and located on the basal side of the cell. Ciliated columnar epithelium is composed of simple columnar epithelial cells that display cilia on their apical surfaces. **36** Blood is a fluid connective tissue, a variety of specialized cells that circulate in a watery fluid containing salts, nutrients, and dissolved proteins in a liquid extracellular matrix. Blood contains formed elements derived from bone marrow. Erythrocytes, or red blood cells, transport the gases oxygen and carbon dioxide. Leukocytes, or white blood cells, are responsible for the defense of the organism against potentially harmful microorganisms or molecules. Platelets are cell fragments involved in blood clotting. Some cells have the ability to cross the endothelial layer that lines vessels and enter adjacent tissues. Nutrients, salts, and waste are dissolved in the liquid matrix and transported through the body. **37** A layer of dense irregular connective tissue covers cartilage. No blood vessels supply cartilage tissue. Injuries to cartilage heal very slowly because cells and nutrients needed for repair diffuse slowly to the injury site. **38** The cells in the dish are cardiomyocytes, cardiac muscle cells. They have an intrinsic ability to contract. When they link up, they form intercalating discs that allow the cells to communicate with each other and begin contracting in synchrony. **39** Under the light microscope, cells appear striated due to the arrangement of the contractile proteins actin and myosin. **40** Neurons are well suited for the transmission of nerve impulses because short extensions, dendrites, receive impulses from other neurons, while a long tail extension, an axon, carries electrical impulses away from the cell to other neurons. **41** Astrocytes regulate ions and uptake and/or breakdown of some neurotransmitters and contribute to the formation of the blood-brain-barrier. **42** These symptoms would indicate that infection is present. **43** Since NSAIDs or other anti-inflammatory drugs inhibit the formation of blood clots, regular and prolonged use of these drugs may promote internal bleeding, such as bleeding in the stomach. Excessive levels of cortisol would suppress inflammation, which could slow the wound healing process. **44** The genetic makeup and the lifestyle of each individual are factors which determine the degree of decline in cells, tissues, and organs as an individual ages. **45** All cells experience changes with aging. They become larger, and many cannot divide and regenerate. Because of alterations in cell membranes, transport of oxygen and nutrients into the cell and removal of carbon dioxide and waste products are not as efficient in the elderly. Cells lose their ability to function, or they begin to function abnormally, leading to disease and cancer.

## Chapter 5

**1** The epidermis provides protection, the dermis provides support and flexibility, and the hypodermis (fat layer) provides insulation and padding. **2** **Figure 5.4** These cells do not have nuclei, so you can deduce that they are dead. They appear to be sloughing off. **3** **Figure 5.6** These cells have desmosomes, which give the cells their spiny appearance. **4** There are none. **5** D **6** A **7** C **8** B **9** C **10** C **11** D **12** B **13** B **14** B **15** A **16** C **17** C **18** A **19** C **20** C **21** C **22** D **23** B **24** C **25** The pigment melanin, produced by melanocytes, is primarily responsible for skin color. Melanin comes in different shades of brown and black. Individuals with darker skin have darker, more abundant melanin, whereas fair-skinned individuals have a lighter shade of skin and less melanin. Exposure to UV irradiation stimulates the melanocytes to produce and secrete more melanin. **26** As the cells move into the stratum spinosum, they begin the synthesis of keratin and extend cell processes, desmosomes, which link the cells. As the stratum basale continues to produce new cells, the keratinocytes of the stratum spinosum are pushed into the stratum granulosum. The cells become flatter, their cell membranes thicken, and they generate large amounts of the proteins keratin and keratohyalin. The nuclei and other cell organelles disintegrate as the cells die, leaving behind the keratin, keratohyalin, and cell membranes that form the stratum lucidum and the stratum corneum. The keratinocytes in these layers are mostly dead and flattened. Cells in the stratum corneum are periodically shed. **27** Eccrine sweat glands are all over the body, especially the forehead and palms of the hand. They release a watery sweat, mixed with some metabolic waste and antibodies. Apocrine glands are associated with hair follicles. They are larger than eccrine sweat glands and lie deeper in the dermis, sometimes even reaching the hypodermis. They release a thicker sweat that is often decomposed by bacteria on the skin, resulting in an unpleasant odor. **28** Nails are composed of densely packed dead keratinocytes. They protect the fingers and toes from mechanical stress. The nail body is formed on the nail bed, which is at the nail root. Nail folds, folds of skin that overlap the nail on its side, secure the nail to the body. The crescent-shaped region at the base of the nail is the lunula. **29** Sweating cools the body when it becomes warm. When the body temperature rises, such as when exercising on a hot day, the dermal blood vessels dilate, and the sweat glands begin to secrete more sweat. The evaporation of the sweat from the surface of the skin cools the body by dissipating heat. **30** When the core body temperature drops, the body switches to heat-conservation mode. This can include an inhibition to excessive sweating and

a decrease of blood flow to the papillary layers of the skin. This reduction of blood flow helps conserve body heat. **31** Acne results from a blockage of sebaceous glands by sebum. The blockage causes blackheads to form, which are susceptible to infection. The infected tissue then becomes red and inflamed. Teenagers experience this at high rates because the sebaceous glands become active during puberty. Hormones that are especially active during puberty stimulate the release of sebum, leading in many cases to blockages. **32** Scars are made of collagen and do not have the cellular structure of normal skin. The tissue is fibrous and does not allow for the regeneration of accessory structures, such as hair follicles, and sweat or sebaceous glands.

## Chapter 6

**1** B **2** D **3** C **4** A **5** B **6** B **7** B **8** D **9** A **10** A **11** C **12** C **13** B **14** A **15** C **16** D **17** C **18** C **19** A **20** C **21** D **22** B **23** D **24** A **25** B **26** C **27** B **28** B **29** D **30** B **31** C **32** A **33** A **34** C **35** A **36** D **37** D **38** A **39** B **40** It supports the body. The rigid, yet flexible skeleton acts as a framework to support the other organs of the body. It facilitates movement. The movable joints allow the skeleton to change shape and positions; that is, move. It protects internal organs. Parts of the skeleton enclose or partly enclose various organs of the body including our brain, ears, heart, and lungs. Any trauma to these organs has to be mediated through the skeletal system. It produces blood cells. The central cavity of long bones is filled with marrow. The red marrow is responsible for forming red and white blood cells. It stores and releases minerals and fat. The mineral component of bone, in addition to providing hardness to bone, provides a mineral reservoir that can be tapped as needed. Additionally, the yellow marrow, which is found in the central cavity of long bones along with red marrow, serves as a storage site for fat. **41** Structurally, a tarsal is a short bone, meaning its length, width, and thickness are about equal, while a metatarsal is a long bone whose length is greater than its width. Functionally, the tarsal provides limited motion, while the metatarsal acts as a lever. **42** Structurally, the femur is a long bone, meaning its length is greater than its width, while the patella, a sesamoid bone, is small and round. Functionally, the femur acts as a lever, while the patella protects the patellar tendon from compressive forces. **43** If the articular cartilage at the end of one of your long bones were to deteriorate, which is actually what happens in osteoarthritis, you would experience joint pain at the end of that bone and limitation of motion at that joint because there would be no cartilage to reduce friction between adjacent bones and there would be no cartilage to act as a shock absorber. **44** The densely packed concentric rings of matrix in compact bone are ideal for resisting compressive forces, which is the function of compact bone. The open spaces of the trabeculated network of spongy bone allow spongy bone to support shifts in weight distribution, which is the function of spongy bone. **45** In intramembranous ossification, bone develops directly from sheets of mesenchymal connective tissue, but in endochondral ossification, bone develops by replacing hyaline cartilage. Intramembranous ossification is complete by the end of the adolescent growth spurt, while endochondral ossification lasts into young adulthood. The flat bones of the face, most of the cranial bones, and a good deal of the clavicles (collarbones) are formed via intramembranous ossification, while bones at the base of the skull and the long bones form via endochondral ossification. **46** A single primary ossification center is present, during endochondral ossification, deep in the periosteal collar. Like the primary ossification center, secondary ossification centers are present during endochondral ossification, but they form later, and there are two of them, one in each epiphysis. **47** In closed reduction, the broken ends of a fractured bone can be reset without surgery. Open reduction requires surgery to return the broken ends of the bone to their correct anatomical position. A partial fracture would likely require closed reduction. A compound fracture would require open reduction. **48** The internal callus is produced by cells in the endosteum and is composed of a fibrocartilaginous matrix. The external callus is produced by cells in the periosteum and consists of hyaline cartilage and bone. **49** Since maximum bone mass is achieved by age 30, I would want this patient to have adequate calcium and vitamin D in her diet. To do this, I would recommend ingesting milk and other dairy foods, green leafy vegetables, and intact canned sardines so she receives sufficient calcium. Intact salmon would be a good source for calcium and vitamin D. Other fatty fish would also be a good vitamin D source. **50** Astronauts floating in space were not exerting significant pressure on their bones; they were “weightless.” Without the force of gravity exerting pressure on the bones, bone mass was lost. To alleviate this condition, astronauts now do resistive exercise designed to apply forces to the bones and thus help keep them healthy. **51** Vitamin D is required for calcium absorption by the gut. Low vitamin D could lead to insufficient levels of calcium in the blood so the calcium is being released from the bones. The reduction of calcium from the bones can make them weak and subject to fracture. **52** Under “normal” conditions, receptors in the parathyroid glands bind blood calcium. When the receptors are full, the parathyroid gland stops secreting PTH. In the condition described, the parathyroid glands are not responding to the signal that there is sufficient calcium in the blood and they keep releasing PTH, which causes the bone to release more calcium into the blood. Ultimately, the bones become fragile and hypercalcemia can result.

## Chapter 7

**1** The sphenoid bone joins with most other bones of the skull. It is centrally located, where it forms portions of the rounded brain case and cranial base. **2** A basilar fracture may damage an artery entering the skull, causing bleeding in the brain. **3** Osteoporosis causes thinning and weakening of the vertebral bodies. When this occurs in thoracic vertebrae, the bodies may collapse producing kyphosis, an enhanced anterior curvature of the thoracic vertebral column. **4** Lifting a heavy object can cause an intervertebral disc in the lower back to bulge and compress a spinal nerve as it exits through the intervertebral foramen, thus producing pain in those regions of the lower limb supplied by that nerve. **5** The anterior longitudinal ligament is thickest in the thoracic region of the vertebral column, while the supraspinous ligament is thickest in the lumbar region. **6** Bones on the top and sides of the skull develop when fibrous membrane areas ossify (convert) into bone. The bones of the limbs, ribs, and vertebrae develop when cartilage models of the bones ossify into bone. **7** D **8** C **9** B **10** A **11** B **12** D **13** A **14** A **15** D **16** A **17** B **18** C **19** A **20** A **21** B **22** D **23** A **24** D **25** B **26** D **27** The axial skeleton forms the vertical axis of the body and includes the bones of the head, neck, back, and chest of the body. It consists of 80 bones that include the skull, vertebral column, and thoracic cage. The appendicular skeleton consists of 126 bones and includes all bones of the upper and lower limbs. **28** The axial skeleton supports

the head, neck, back, and chest of the body and allows for movements of these body regions. It also gives bony protections for the brain, spinal cord, heart, and lungs; stores fat and minerals; and houses the blood-cell producing tissue. **29** The brain case is that portion of the skull that surrounds and protects the brain. It is subdivided into the rounded top of the skull, called the calvaria, and the base of the skull. There are eight bones that form the brain case. These are the paired parietal and temporal bones, plus the unpaired frontal, occipital, sphenoid, and ethmoid bones. The facial bones support the facial structures, and form the upper and lower jaws, nasal cavity, nasal septum, and orbit. There are 14 facial bones. These are the paired maxillary, palatine, zygomatic, nasal, lacrimal, and inferior nasal conchae bones, and the unpaired vomer and mandible bones. **30** The coronal suture passes across the top of the anterior skull. It unites the frontal bone anteriorly with the right and left parietal bones. The sagittal suture runs at the midline on the top of the skull. It unites the right and left parietal bones with each other. The squamous suture is a curved suture located on the lateral side of the skull. It unites the squamous portion of the temporal bone to the parietal bone. The lambdoid suture is located on the posterior skull and has an inverted V-shape. It unites the occipital bone with the right and left parietal bones. **31** The anterior cranial fossa is the shallowest of the three cranial fossae. It extends from the frontal bone anteriorly to the lesser wing of the sphenoid bone posteriorly. It is divided at the midline by the crista galli and cribriform plates of the ethmoid bone. The middle cranial fossa is located in the central skull, and is deeper than the anterior fossa. The middle fossa extends from the lesser wing of the sphenoid bone anteriorly to the petrous ridge posteriorly. It is divided at the midline by the sella turcica. The posterior cranial fossa is the deepest fossa. It extends from the petrous ridge anteriorly to the occipital bone posteriorly. The large foramen magnum is located at the midline of the posterior fossa. **32** There are two bony parts of the nasal septum in the dry skull. The perpendicular plate of the ethmoid bone forms the superior part of the septum. The vomer bone forms the inferior and posterior parts of the septum. In the living skull, the septal cartilage completes the septum by filling in the anterior area between the bony components and extending outward into the nose. **33** The adult vertebral column consists of 24 vertebrae, plus the sacrum and coccyx. The vertebrae are subdivided into cervical, thoracic, and lumbar regions. There are seven cervical vertebrae (C1–C7), 12 thoracic vertebrae (T1–T12), and five lumbar vertebrae (L1–L5). The sacrum is derived from the fusion of five sacral vertebrae and the coccyx is formed by the fusion of four small coccygeal vertebrae. **34** A typical vertebra consists of an anterior body and a posterior vertebral arch. The body serves for weight bearing. The vertebral arch surrounds and protects the spinal cord. The vertebral arch is formed by the pedicles, which are attached to the posterior side of the vertebral body, and the lamina, which come together to form the top of the arch. A pair of transverse processes extends laterally from the vertebral arch, at the junction between each pedicle and lamina. The spinous process extends posteriorly from the top of the arch. A pair of superior articular processes project upward and a pair of inferior articular processes project downward. Together, the notches found in the margins of the pedicles of adjacent vertebrae form an intervertebral foramen. **35** The sacrum is a single, triangular-shaped bone formed by the fusion of five sacral vertebrae. On the posterior sacrum, the median sacral crest is derived from the fused spinous processes, and the lateral sacral crest results from the fused transverse processes. The sacral canal contains the sacral spinal nerves, which exit via the anterior (ventral) and posterior (dorsal) sacral foramina. The sacral promontory is the anterior lip. The sacrum also forms the posterior portion of the pelvis. **36** An intervertebral disc fills in the space between adjacent vertebrae, where it provides padding and weight-bearing ability, and allows for movements between the vertebrae. It consists of an outer anulus fibrosus and an inner nucleus pulposus. The anulus fibrosus strongly anchors the adjacent vertebrae to each other, and the high water content of the nucleus pulposus resists compression for weight bearing and can change shape to allow for vertebral column movements. **37** The anterior longitudinal ligament is attached to the vertebral bodies on the anterior side of the vertebral column. The supraspinous ligament is located on the posterior side, where it interconnects the thoracic and lumbar spinous processes. In the posterior neck, this ligament expands to become the nuchal ligament, which attaches to the cervical spinous processes and the base of the skull. The posterior longitudinal ligament and ligamentum flavum are located inside the vertebral canal. The posterior longitudinal ligament unites the posterior sides of the vertebral bodies. The ligamentum flavum unites the lamina of adjacent vertebrae. **38** The thoracic cage is formed by the 12 pairs of ribs with their costal cartilages and the sternum. The ribs are attached posteriorly to the 12 thoracic vertebrae and most are anchored anteriorly either directly or indirectly to the sternum. The thoracic cage functions to protect the heart and lungs. **39** The sternum consists of the manubrium, body, and xiphoid process. The manubrium forms the expanded, superior end of the sternum. It has a jugular (suprasternal) notch, a pair of clavicular notches for articulation with the clavicles, and receives the costal cartilage of the first rib. The manubrium is joined to the body of the sternum at the sternal angle, which is also the site for attachment of the second rib costal cartilages. The body receives the costal cartilage attachments for ribs 3–7. The small xiphoid process forms the inferior tip of the sternum. **40** A typical rib is a flattened, curved bone. The head of a rib is attached posteriorly to the costal facets of the thoracic vertebrae. The rib tubercle articulates with the transverse process of a thoracic vertebra. The angle is the area of greatest rib curvature and forms the largest portion of the thoracic cage. The body (shaft) of a rib extends anteriorly and terminates at the attachment to its costal cartilage. The shallow costal groove runs along the inferior margin of a rib and carries blood vessels and a nerve. **41** Ribs are classified based on if and how their costal cartilages attach to the sternum. True (vertebrosternal) ribs are ribs 1–7. The costal cartilage for each of these attaches directly to the sternum. False (vertebrochondral) ribs, 8–12, are attached either indirectly or not at all to the sternum. Ribs 8–10 are attached indirectly to the sternum. For these ribs, the costal cartilage of each attaches to the cartilage of the next higher rib. The last false ribs (11–12) are also called floating (vertebral) ribs, because these ribs do not attach to the sternum at all. Instead, the ribs and their small costal cartilages terminate within the muscles of the lateral abdominal wall. **42** The brain-case bones that form the top and sides of the skull are produced by intramembranous ossification. In this, mesenchyme from the sclerotome portion of the somites accumulates at the site of the future bone and differentiates into bone-producing cells. These generate areas of bone that are initially separated by wide regions of fibrous connective tissue called fontanelles. After birth, as the bones enlarge, the fontanelles disappear. However, the bones remain separated by the sutures, where bone and skull growth can continue until the adult size is obtained. **43** The facial bones and base of the skull arise via the process of endochondral ossification. This process begins with the localized accumulation of mesenchyme tissue at the sites of the future bones. The mesenchyme differentiates into hyaline cartilage, which forms a cartilage model of the future bone. The cartilage allows for growth and enlargement of the model. It is gradually converted into bone over time. **44** The vertebrae, ribs, and sternum all develop via the process of endochondral ossification. Mesenchyme tissue from the sclerotome portion of the somites accumulates on either side of the notochord and produces hyaline cartilage models for each

vertebra. In the thorax region, a portion of this cartilage model splits off to form the ribs. Similarly, mesenchyme forms cartilage models for the right and left halves of the sternum. The ribs then become attached anteriorly to the developing sternum, and the two halves of sternum fuse together. Ossification of the cartilage model into bone occurs within these structures over time. This process continues until each is converted into bone, except for the sternal ends of the ribs, which remain as the costal cartilages.

## Chapter 8

**1** A fracture through the joint surface of the distal radius may make the articulating surface of the radius rough or jagged. This can then cause painful movements involving this joint and the early development of arthritis. Surgery can return the joint surface to its original smoothness, thus allowing for the return of normal function. **2** The hand has a proximal transverse arch, a distal transverse arch, and a longitudinal arch. These allow the hand to conform to objects being held. These arches maximize the amount of surface contact between the hand and object, which enhances stability and increases sensory input. **3** Surgery may be required if the fracture is unstable, meaning that the broken ends of the radius won't stay in place to allow for proper healing. In this case, metal plates and screws can be used to stabilize the fractured bone. **4** The obturator foramen is located between the ischium and the pubis. The superior and inferior pubic rami contribute to the boundaries of the obturator foramen. **5** A hole is drilled into the greater trochanter, the bone marrow (medullary) space inside the femur is enlarged, and finally an intramedullary rod is inserted into the femur. This rod is then anchored to the bone with screws. **6** Metal cutting jigs are attached to the bones to ensure that the bones are cut properly prior to the attachment of prosthetic components. **7** The proximal group of tarsal bones includes the calcaneus and talus bones, the navicular bone is intermediate, and the distal group consists of the cuboid bone plus the medial, intermediate, and lateral cuneiform bones. **8** A bunion results from the deviation of the big toe toward the second toe, which causes the distal end of the first metatarsal bone to stick out. A bunion may also be caused by prolonged pressure on the foot from pointed shoes with a narrow toe box that compresses the big toe and pushes it toward the second toe. **9** (a) The upper limb bud initially appears on day 26 as the upper limb ridge. This becomes the upper limb bud by day 28. (b) The handplate and footplate appear at day 36. (c) Rotation of the upper and lower limbs begins during the seventh week (day 48). **10** B **11** C **12** D **13** A **14** C **15** D **16** A **17** C **18** D **19** B **20** B **21** A **22** B **23** C **24** A **25** B **26** C **27** D **28** C **29** C **30** D **31** C **32** A **33** The clavicle extends laterally across the anterior shoulder and can be palpated along its entire length. At its lateral end, the clavicle articulates with the acromion of the scapula, which forms the bony tip of the shoulder. The acromion is continuous with the spine of the scapula, which can be palpated medially and posteriorly along its length. Together, the clavicle, acromion, and spine of the scapula form a V-shaped line that serves as an important area for muscle attachment. **34** A blow to the shoulder or falling onto an outstretched hand passes strong forces through the scapula to the clavicle and sternum. A hard fall may thus cause a fracture of the clavicle (broken collarbone) or may injure the ligaments of the acromioclavicular joint. In a severe case, the coracoclavicular ligament may also rupture, resulting in complete dislocation of the acromioclavicular joint (a "shoulder separation"). **35** As you push against the car, forces will pass from the metacarpal bones of your hand into the carpal bones at the base of your hand. Forces will then pass through the midcarpal and radiocarpal joints into the radius and ulna bones of the forearm. These will pass the force through the elbow joint into the humerus of the arm, and then through the glenohumeral joint into the scapula. The force will travel through the acromioclavicular joint into the clavicle, and then through the sternoclavicular joint into the sternum, which is part of the axial skeleton. **36** The base of the hand is formed by the eight carpal bones arranged in two rows (distal and proximal) of four bones each. The proximal row contains (from lateral to medial) the scaphoid, lunate, triquetrum, and pisiform bones. The distal row contains (from medial to lateral) the hamate, capitate, trapezoid, and trapezium bones. (Use the mnemonic "So Long To Pinky, Here Comes The Thumb" to remember this sequence). The rows of the proximal and distal carpal bones articulate with each other at the midcarpal joint. The palm of the hand contains the five metacarpal bones, which are numbered 1–5 starting on the thumb side. The proximal ends of the metacarpal bones articulate with the distal row of the carpal bones. The distal ends of the metacarpal bones articulate with the proximal phalanx bones of the thumb and fingers. The thumb (digit 1) has both a proximal and distal phalanx bone. The fingers (digits 2–5) all contain proximal, middle, and distal phalanges. **37** The pelvis is formed by the combination of the right and left hip bones, the sacrum, and the coccyx. The auricular surfaces of each hip bone articulate with the auricular surface of the sacrum to form the sacroiliac joint. This joint is supported on either side by the strong anterior and posterior sacroiliac ligaments. The right and left hip bones converge anteriorly, where the pubic bodies articulate with each other to form the pubic symphysis joint. The sacrum is also attached to the hip bone by the sacrospinous ligament, which spans the sacrum to the ischial spine, and the sacrotuberous ligament, which runs from the sacrum to the ischial tuberosity. The coccyx is attached to the inferior end of the sacrum. **38** Compared to the male, the female pelvis is wider to accommodate childbirth. Thus, the female pelvis has greater distances between the anterior superior iliac spines and between the ischial tuberosities. The greater width of the female pelvis results in a larger subpubic angle. This angle, formed by the anterior convergence of the right and left ischiopubic rami, is larger in females (greater than 80 degrees) than in males (less than 70 degrees). The female sacral promontory does not project anteriorly as far as it does in males, which gives the pelvic brim (pelvic inlet) of the female a rounded or oval shape. The lesser pelvic cavity is wider and more shallow in females, and the pelvic outlet is larger than in males. Thus, the greater width of the female pelvis, with its larger pelvic inlet, lesser pelvis, and pelvic outlet, are important for childbirth because the baby must pass through the pelvis during delivery. **39** The lower limb is divided into three regions. The thigh is the region located between the hip and knee joints. It contains the femur and the patella. The hip joint is formed by the articulation between the acetabulum of the hip bone and the head of the femur. The leg is the region between the knee and ankle joints, and contains the tibia (medially) and the fibula (laterally). The knee joint is formed by the articulations between the medial and lateral condyles of the femur, and the medial and lateral condyles of the tibia. Also associated with the knee is the patella, which articulates with the patellar surface of the distal femur. The foot is found distal to the ankle and contains 26 bones. The ankle joint is formed by the articulations between the talus bone of the foot and the distal end of the tibia, the medial malleolus of the tibia, and the lateral malleolus of the fibula. The posterior foot contains the seven tarsal bones, which are the talus, calcaneus, navicular, cuboid, and the medial, intermediate, and lateral cuneiform bones. The anterior foot consists of the five metatarsal bones, which are numbered 1–5 starting on the medial side of the foot. The toes contain 14 phalanx bones, with the big toe (toe number 1) having a proximal and

a distal phalanx, and the other toes having proximal, middle, and distal phalanges. **40** The talus bone articulates superiorly with the tibia and fibula at the ankle joint, with body weight passed from the tibia to the talus. Body weight from the talus is transmitted to the ground by both ends of the medial and lateral longitudinal foot arches. Weight is passed posteriorly through both arches to the calcaneus bone, which forms the heel of the foot and is in contact with the ground. On the medial side of the foot, body weight is passed anteriorly from the talus bone to the navicular bone, and then to the medial, intermediate, and lateral cuneiform bones. The cuneiform bones pass the weight anteriorly to the first, second, and third metatarsal bones, whose heads (distal ends) are in contact with the ground. On the lateral side, body weight is passed anteriorly from the talus through the calcaneus, cuboid, and fourth and fifth metatarsal bones. The talus bone thus transmits body weight posteriorly to the calcaneus and anteriorly through the navicular, cuneiform, and cuboid bones, and metatarsals one through five. **41** A radiograph (X-ray image) of a child's femur will show the epiphyseal plates associated with each secondary ossification center. These plates of hyaline cartilage will appear dark in comparison to the white imaging of the ossified bone. Since each epiphyseal plate appears and disappears at a different age, the presence or absence of these plates can be used to give an approximate age for the child. For example, the epiphyseal plate located at the base of the lesser trochanter of the femur appears at age 9–10 years and disappears at puberty (approximately 11 years of age). Thus, a child's radiograph that shows the presence of the lesser trochanter epiphyseal plate indicates an approximate age of 10 years. **42** Unlike other bones of the appendicular skeleton, the clavicle develops by the process of intramembranous ossification. In this process, embryonic mesenchyme accumulates at the site of the future bone and then differentiates directly into bone-producing tissue. Because of this direct and early production of bone, the clavicle is the first bone of the skeleton to begin to ossify. However, the growth and enlargement of the clavicle continues throughout childhood and adolescence, and thus, it is not fully ossified until 25 years of age.

## Chapter 9

**1** Although they are still growing, the carpal bones of the wrist area do not show an epiphyseal plate. Instead of elongating, these bones grow in diameter by adding new bone to their surfaces. **2** Ball-and-socket joint. **3** Gout is due to the accumulation of uric acid crystals in the body. Usually these accumulate within joints, causing joint pain. This patient also had crystals that accumulated in the space next to his spinal cord, thus compressing the spinal cord and causing muscle weakness. **4** The most common cause of hip disability is osteoarthritis, a chronic disease in which the articular cartilage of the joint wears away, resulting in severe hip pain and stiffness. **5** The immune system malfunctions and attacks healthy cells in the lining of your joints. This causes inflammation and pain in the joints and surrounding tissues. **6** Dorsiflexion of the foot at the ankle decreases the angle of the ankle joint, while plantar flexion increases the angle of the ankle joint. **7** The first motion is rotation (hinging) of the mandible, but this only produces about 20 mm (0.78 in) of mouth opening. **8** The shoulder joint is a ball-and-socket joint that allows for flexion-extension, abduction-adduction, medial rotation, lateral rotation, and circumduction of the humerus. **9** The glenoid labrum is wedge-shaped in cross-section. This is important because it creates an elevated rim around the glenoid cavity, which creates a deeper socket for the head of the humerus to fit into. **10** The structures that stabilize the elbow include the coronoid process, the radial (lateral) collateral ligament, and the anterior portion of the ulnar (medial) collateral ligament. **11** The articular cartilage functions to absorb shock and to provide an extremely smooth surface that makes movement between bones easy, without damaging the bones. **12** An intracapsular fracture of the neck of the femur can result in disruption of the arterial blood supply to the head of the femur, which may lead to avascular necrosis of the femoral head. **13** The articular cartilage is thickest in the upper and back part of the acetabulum, the socket portion of the hip joint. These regions receive most of the force from the head of the femur during walking and running. **14** There are five ligaments associated with the knee joint. The tibial collateral ligament is located on the medial side of the knee and the fibular collateral ligament is located on the lateral side. The anterior and posterior cruciate ligaments are located inside the knee joint. **15** The anterior cruciate ligament prevents the tibia from sliding too far forward in relation to the femur and the posterior cruciate ligament keeps the tibia from sliding too far backward. **16** The anterior cruciate ligament (ACL) is most commonly injured when traumatic force is applied to the knee during a twisting motion or when side standing or landing from a jump. **17** The ligaments of the lateral ankle are the anterior and posterior talofibular ligaments and the calcaneofibular ligament. These ligaments support the ankle joint and resist excess inversion of the foot. **18** Because of the square shape of the ankle joint, it has been compared to a mortise-and-tendon type of joint. **19** An inversion ankle sprain may injure all three ligaments located on the lateral side of the ankle. The sequence of injury would be the anterior talofibular ligament first, followed by the calcaneofibular ligament second, and finally, the posterior talofibular ligament third. **20** C **21** B **22** A **23** D **24** A **25** A **26** D **27** C **28** B **29** D **30** A **31** A **32** A **33** B **34** C **35** C **36** D **37** D **38** B **39** A **40** A **41** C **42** D **43** A **44** C **45** C **46** A **47** D **48** C **49** B **50** B **51** C **52** A **53** Functional classification of joints is based on the degree of mobility exhibited by the joint. A synarthrosis is an immobile or nearly immobile joint. An example is the manubriosternal joint or the joints between the skull bones surrounding the brain. An amphiarthrosis is a slightly moveable joint, such as the pubic symphysis or an intervertebral cartilaginous joint. A diarthrosis is a freely moveable joint. These are subdivided into three categories. A uniaxial diarthrosis allows movement within a single anatomical plane or axis of motion. The elbow joint is an example. A biaxial diarthrosis, such as the metacarpophalangeal joint, allows for movement along two planes or axes. The hip and shoulder joints are examples of a multiaxial diarthrosis. These allow movements along three planes or axes. **54** The functional needs of joints vary and thus joints differ in their degree of mobility. A synarthrosis, which is an immobile joint, serves to strongly connect bones thus protecting internal organs such as the heart or brain. A slightly moveable amphiarthrosis provides for small movements, which in the vertebral column can add together to yield a much larger overall movement. The freedom of movement provided by a diarthrosis can allow for large movements, such as is seen with most joints of the limbs. **55** Narrow fibrous joints are found at a suture, gomphosis, or syndesmosis. A suture is the fibrous joint that joins the bones of the skull to each other (except the mandible). A gomphosis is the fibrous joint that anchors each tooth to its bony socket within the upper or lower jaw. The tooth is connected to the bony jaw by periodontal ligaments. A narrow syndesmosis is found at the distal tibiofibular joint where the bones are united by fibrous connective tissue and ligaments. A syndesmosis can also form a wide fibrous joint where the shafts of two parallel bones are connected by a broad interosseous membrane. The radius

and ulna bones of the forearm and the tibia and fibula bones of the leg are united by interosseous membranes. **56** The teeth are anchored into their sockets within the bony jaws by the periodontal ligaments. This is a gomphosis type of fibrous joint. In scurvy, collagen production is inhibited and the periodontal ligaments become weak. This will cause the teeth to become loose or even to fall out. **57** Cartilaginous joints are where the adjacent bones are joined by cartilage. At a synchondrosis, the bones are united by hyaline cartilage. The epiphyseal plate of growing long bones and the first sternocostal joint that unites the first rib to the sternum are examples of synchondroses. At a symphysis, the bones are joined by fibrocartilage, which is strong and flexible. Symphysis joints include the intervertebral symphysis between adjacent vertebrae and the pubic symphysis that joins the pubic portions of the right and left hip bones. **58** The first sternocostal joint is a synchondrosis type of cartilaginous joint in which hyaline cartilage unites the first rib to the manubrium of the sternum. This forms an immobile (synarthrosis) type of joint. The pubic symphysis is a slightly mobile (amphiarthrosis) cartilaginous joint, where the pubic portions of the right and left hip bones are united by fibrocartilage, thus forming a symphysis. **59** All synovial joints have a joint cavity filled with synovial fluid that is the site at which the bones of the joint articulate with each other. The articulating surfaces of the bones are covered by articular cartilage, a thin layer of hyaline cartilage. The walls of the joint cavity are formed by the connective tissue of the articular capsule. The synovial membrane lines the interior surface of the joint cavity and secretes the synovial fluid. Synovial joints are directly supported by ligaments, which span between the bones of the joint. These may be located outside of the articular capsule (extrinsic ligaments), incorporated or fused to the wall of the articular capsule (intrinsic ligaments), or found inside of the articular capsule (intracapsular ligaments). Ligaments hold the bones together and also serve to resist or prevent excessive or abnormal movements of the joint. **60** Direct support for a synovial joint is provided by ligaments that strongly unite the bones of the joint and serve to resist excessive or abnormal movements. Some joints, such as the sternoclavicular joint, have an articular disc that is attached to both bones, where it provides direct support by holding the bones together. Indirect joint support is provided by the muscles and their tendons that act across a joint. Muscles will increase their contractile force to help support the joint by resisting forces acting on it. **61** Ball-and-socket joints are multiaxial joints that allow for flexion and extension, abduction and adduction, circumduction, and medial and lateral rotation. **62** To cross your arms, you need to use both your shoulder and elbow joints. At the shoulder, the arm would need to flex and medially rotate. At the elbow, the forearm would need to be flexed. **63** The shoulder joint allows for a large range of motion. The primary support for the shoulder joint is provided by the four rotator cuff muscles. These muscles serve as “dynamic ligaments” and thus can modulate their strengths of contraction as needed to hold the head of the humerus in position at the glenoid fossa. Additional but weaker support comes from the coracohumeral ligament, an intrinsic ligament that supports the superior aspect of the shoulder joint, and the glenohumeral ligaments, which are intrinsic ligaments that support the anterior side of the joint. **64** A strong blow to the lateral side of the extended knee will cause the medial side of the knee joint to open, resulting in a sequence of three injuries. First will be damage to the tibial collateral ligament. Since the medial meniscus is attached to the tibial collateral ligament, the meniscus is also injured. The third structure injured would be the anterior cruciate ligament. **65** Mesenchyme gives rise to cartilage models of the future limb bones. An area called the joint interzone located between adjacent cartilage models will become a synovial joint. The cells at the center of the interzone die, thus producing the joint cavity. Additional mesenchyme cells at the periphery of the interzone become the articular capsule. **66** Intramembranous ossification is the process by which mesenchymal cells differentiate directly into bone producing cells. This process produces the bones that form the top and sides of the skull. The remaining skull bones and the bones of the limbs are formed by endochondral ossification. In this, mesenchymal cells differentiate into hyaline cartilage cells that produce a cartilage model of the future bone. The cartilage is then gradually replaced by bone tissue over a period of many years, during which the cartilage of the epiphyseal plate can continue to grow to allow for enlargement or lengthening of the bone.

## Chapter 10

**1** (a) Z-lines. (b) Sarcomeres. (c) This is the arrangement of the actin and myosin filaments in a sarcomere. (d) The alternating strands of actin and myosin filaments. **2** (a) It is the number of skeletal muscle fibers supplied by a single motor neuron. (b) A large motor unit has one neuron supplying many skeletal muscle fibers for gross movements, like the Temporalis muscle, where 1000 fibers are supplied by one neuron. A small motor has one neuron supplying few skeletal muscle fibers for very fine movements, like the extraocular eye muscles, where six fibers are supplied by one neuron. (c) To avoid prolongation of muscle contraction. **3** (a) The T-tubules are inward extensions of the sarcolemma that trigger the release of $Ca^{++}$ from SR during an Action Potential. (b) $Ca^{++}$ binds to tropomyosin, and this slides the tropomyosin rods away from the binding sites. **4** D **5** B **6** C **7** B **8** A **9** D **10** D **11** B **12** C **13** C **14** D **15** C **16** B **17** A **18** B **19** D **20** A **21** B **22** C **23** A **24** D **25** C **26** A **27** A **28** C **29** D **30** It allows muscle to return to its original length during relaxation after contraction. **31** Muscles would lose their integrity during powerful movements, resulting in muscle damage. **32** When a muscle contracts, the force of movement is transmitted through the tendon, which pulls on the bone to produce skeletal movement. **33** Produce movement of the skeleton, maintain posture and body position, support soft tissues, encircle openings of the digestive, urinary, and other tracts, and maintain body temperature. **34** The opening of voltage-gated sodium channels, followed by the influx of $Na^{+}$, transmits an Action Potential after the membrane has sufficiently depolarized. The delayed opening of potassium channels allows $K^{+}$ to exit the cell, to repolarize the membrane. **35** Without T-tubules, action potential conduction into the interior of the cell would happen much more slowly, causing delays between neural stimulation and muscle contraction, resulting in slower, weaker contractions. **36** Dark A bands and light I bands repeat along myofibrils, and the alignment of myofibrils in the cell cause the entire cell to appear striated. **37** Without ATP, the myosin heads cannot detach from the actin-binding sites. All of the “stuck” cross-bridges result in muscle stiffness. In a live person, this can cause a condition like “writer’s cramps.” In a recently dead person, it results in rigor mortis. **38** Eyes require fine movements and a high degree of control, which is permitted by having fewer muscle fibers associated with a neuron. **39** The length, size and types of muscle fiber and the frequency of neural stimulation contribute to the amount of tension produced in an individual muscle fiber. **40** Creatine phosphate is used because creatine phosphate and ADP are converted very quickly into ATP by creatine kinase. Glycolysis cannot generate ATP as quickly as creatine phosphate. **41**

Aerobic respiration is much more efficient than anaerobic glycolysis, yielding 36 ATP per molecule of glucose, as opposed to two ATP produced by glycolysis. **42** Endurance training modifies slow fibers to make them more efficient by producing more mitochondria to enable more aerobic metabolism and more ATP production. Endurance exercise can also increase the amount of myoglobin in a cell and formation of more extensive capillary networks around the fiber. **43** Resistance exercises affect muscles by causing the formation of more actin and myosin, increasing the structure of muscle fibers. **44** An action potential could reach a cardiac muscle cell before it has entered the relaxation phase, resulting in the sustained contractions of tetanus. If this happened, the heart would not beat regularly. **45** Cardiac and skeletal muscle cells both contain ordered myofibrils and are striated. Cardiac muscle cells are branched and contain intercalated discs, which skeletal muscles do not have. **46** Smooth muscles can contract over a wider range of resting lengths because the actin and myosin filaments in smooth muscle are not as rigidly organized as those in skeletal and cardiac muscle. **47** Single-unit smooth muscle is found in the walls of hollow organs; multiunit smooth muscle is found in airways to the lungs and large arteries. Single-unit smooth muscle cells contract synchronously, they are coupled by gap junctions, and they exhibit spontaneous action potential. Multiunit smooth cells lack gap junctions, and their contractions are not synchronous. **48** If the damage exceeds what can be repaired by satellite cells, the damaged tissue is replaced by scar tissue, which cannot contract. **49** Smooth muscle tissue can regenerate from stem cells called pericytes, cells found in some small blood vessels. These allow smooth muscle cells to regenerate and repair much more readily than skeletal and cardiac muscle tissue.

## Chapter 11

**1** D **2** A **3** B **4** A **5** C **6** C **7** A **8** A **9** C **10** D **11** D **12** C **13** B **14** B **15** B **16** C **17** A **18** D **19** B **20** C **21** B **22** B **23** A **24** A **25** D **26** B **27** B **28** Fascicle arrangements determine what type of movement a muscle can make. For instance, circular muscles act as sphincters, closing orifices. **29** Muscles work in pairs to facilitate movement of the bones around the joints. Agonists are the prime movers while antagonists oppose or resist the movements of the agonists. Synergists assist the agonists, and fixators stabilize a muscle's origin. **30** Agonists are the prime movers while antagonists oppose or resist the movements of the agonists. Synergists assist the agonists, and fixators stabilize a muscle's origin. **31** In anatomy and physiology, many word roots are Latin or Greek. Portions, or roots, of the word give us clues about the function, shape, action, or location of a muscle. **32** Axial muscles originate on the axial skeleton (the bones in the head, neck, and core of the body), whereas appendicular muscles originate on the bones that make up the body's limbs. **33** The muscles of the anterior neck are arranged to facilitate swallowing and speech. They work on the hyoid bone, with the suprahyoid muscles pulling up and the infrahyoid muscles pulling down. **34** Most skeletal muscles create movement by actions on the skeleton. Facial muscles are different in that they create facial movements and expressions by pulling on the skin—no bone movements are involved. **35** Arranged into layers, the muscles of the abdominal wall are the internal and external obliques, which run on diagonals, the rectus abdominis, which runs straight down the midline of the body, and the transversus abdominis, which wraps across the trunk of the body. **36** Both diaphragms are thin sheets of skeletal muscle that horizontally span areas of the trunk. The diaphragm separating the thoracic and abdominal cavities is the primary muscle of breathing. The pelvic diaphragm, consisting of two paired muscles, the coccygeus and the levator ani, forms the pelvic floor at the inferior end of the trunk. **37** Tendons of the infraspinatus, supraspinatus, teres minor, and the subscapularis form the rotator cuff, which forms a foundation on which the arms and shoulders can be stabilized and move. **38** The muscles that make up the shoulders and upper limbs include the muscles that position the pelvic girdle, the muscles that move the humerus, the muscles that move the forearm, and the muscles that move the wrists, hands, and fingers. **39** The biceps femoris, semimembranosus, and semitendinosus form the hamstrings. The hamstrings flex the leg at the knee joint. **40** The rectus femoris, vastus medialis, vastus lateralis, and vastus intermedius form the quadriceps. The quadriceps muscles extend the leg at the knee joint.

## Chapter 12

**1** MRI uses the relative amount of water in tissue to distinguish different areas, so gray and white matter in the nervous system can be seen clearly in these images. **2** They are part of the somatic nervous system, which is responsible for voluntary movements such as walking or climbing the stairs. **3** Neurons enable thought, perception, and movement. Plants do not move, so they do not need this type of tissue. Microorganisms are too small to have a nervous system. Many are single-celled, and therefore have organelles for perception and movement. **4**Lipid membranes, such as the cell membrane and organelle membranes. **5** Sodium is moving into the cell because of the immense concentration gradient, whereas potassium is moving out because of the depolarization that sodium causes. However, they both move down their respective gradients, toward equilibrium. **6** The properties of electrophysiology are common to all animals, so using the leech is an easier, more humane approach to studying the properties of these cells. There are differences between the nervous systems of invertebrates (such as a leech) and vertebrates, but not for the sake of what these experiments study. **7** A second signal from a separate presynaptic neuron can arrive slightly later, as long as it arrives before the first one dies off, or dissipates. **8** The action potential depolarizes the cell membrane of the axon terminal, which contains the voltage-gated $Ca^{2+}$ channel. That voltage change opens the channel so that $Ca^{2+}$ can enter the axon terminal. Calcium ions make it possible for synaptic vesicles to release their contents through exocytosis. **9** C **10** A **11** D **12** D **13** B **14** A **15** B **16** D **17** A **18** C **19** C **20** D **21** C **22** C **23** A **24** B **25** B **26** A **27** D **28** D **29** B **30** C **31** D **32** D **33** A **34** Running on a treadmill involves contraction of the skeletal muscles in the legs, increase in contraction of the cardiac muscle of the heart, and the production and secretion of sweat in the skin to stay cool. **35** The sensation of taste associated with eating is sensed by nerves in the periphery that are involved in sensory and somatic functions. **36** The disease would target oligodendrocytes. In the CNS, oligodendrocytes provide the myelin for axons. **37** Bipolar cells, because they have one dendrite that receives input and one axon that provides output, would be a direct relay between two other cells. **38** Afferent means "toward," as in sensory information traveling from the periphery into the CNS. Efferent means "away from," as in motor commands that travel from the brain down the spinal cord and out into the periphery. **39** The upper motor neuron would be affected because it is carrying the command from the brain down. **40** The cell membrane must reach threshold before voltage-gated $Na^{+}$ channels open. If threshold is not reached,

those channels do not open, and the depolarizing phase of the action potential does not occur, the cell membrane will just go back to its resting state. **41** Axons of pain sensing sensory neurons are thin and unmyelinated so that it takes longer for that sensation to reach the brain than other sensations. **42** EPSP1 = +5 mV, EPSP2 = +7 mV, EPSP 3 = +10 mV, IPSP1 = -4 mV, IPSP2 = -3 mV. 5 + 7 + 10 – 4 – 3 = +15 mV. **43** Different neurotransmitters have different receptors. Thus, the type of receptor in the postsynaptic cell is what determines which ion channels open. Acetylcholine binding to the nicotinic receptor causes cations to cross the membrane. GABA binding to its receptor causes the anion chloride to cross the membrane.

## Chapter 13

**1** The three regions (forebrain, midbrain, and hindbrain) appear to be approximately equal in size when they are first established, but the midbrain in the adult is much smaller than the others—suggesting that it does not increase in size nearly as much as the forebrain or hindbrain. **2** This is really a matter of opinion, but there are ethical issues to consider when a teenager's behavior results in legal trouble. **3** Both cells are inhibitory. The first cell inhibits the second one. Therefore, the second cell can no longer inhibit its target. This is disinhibition of that target across two synapses. **4** By disinhibiting the subthalamic nucleus, the indirect pathway increases excitation of the globus pallidus internal segment. That, in turn, inhibits the thalamus, which is the opposite effect of the direct pathway that disinhibits the thalamus. **5** There are more motor neurons in the anterior horns that are responsible for movement in the limbs. The cervical enlargement is for the arms, and the lumbar enlargement is for the legs. **6** Energy is needed for the brain to develop and perform higher cognitive functions. That energy is not available for the muscle tissues to develop and function. The hypothesis suggests that humans have larger brains and less muscle mass, and chimpanzees have the smaller brains but more muscle mass. **7** If blood could not get to the middle cerebral artery through the posterior circulation, the blood would flow around the circle of Willis to reach that artery from an anterior vessel. Blood flow would just reverse within the circle. **8** The spinal cord ends in the upper lumbar area of the vertebral column, so a needle inserted lower than that will not damage the nervous tissue of the CNS. **9** The choroid plexuses of the ventricles make CSF. As shown, there is a little of the blue color appearing in each ventricle that is joined by the color flowing from the other ventricles. **10** **Figure 13.20** They derive from the neural crest. **11** **Figure 13.22** The endoneurium surrounding individual nerve fibers is comparable to the endomysium surrounding myofibrils, the perineurium bundling axons into fascicles is comparable to the perimysium bundling muscle fibers into fascicles, and the epineurium surrounding the whole nerve is comparable to the epimysium surrounding the muscle. **12** The optic nerve enters the CNS in its projection from the eyes in the periphery, which means that it crosses through the meninges. Meningitis will include swelling of those protective layers of the CNS, resulting in pressure on the optic nerve, which can compromise vision. **13** C **14** B **15** A **16** D **17** A **18** D **19** C **20** B **21** A **22** B **23** C **24** A **25** A **26** B **27** D **28** C **29** D **30** A **31** D **32** B **33** The retina, a PNS structure in the adult, grows from the diencephalon in the embryonic nervous system. The mature connections from the retina through the optic nerve/tract are to the hypothalamus and thalamus of the diencephalon, and to the midbrain, which developed directly adjacent to the diencephalon as the mesencephalon in the embryo. **34** The neural crest gives rise to PNS structures (such as ganglia) and also to cartilage and bone of the face and cranium. **35** The temporal lobe has sensory functions associated with hearing and vision, as well as being important for memory. A stroke in the temporal lobe can result in specific sensory deficits in these systems (known as agnosias) or losses in memory. **36** A copy of descending input from the cerebrum to the spinal cord, through the pons, and sensory feedback from the spinal cord and special senses like balance, through the medulla, both go to the cerebellum. It can therefore send output through the midbrain that will correct spinal cord control of skeletal muscle movements. **37** The structure is a circular connection of blood vessels, so that blood coming up from one of the arteries can flow in either direction around the circle and avoid any blockage or narrowing of the blood vessels. **38** The nerves that connect the periphery to the CNS pass through these layers of tissue and can be damaged by that inflammation, causing a loss of important neurological functions. **39** The peripheral nervous tissues are out in the body, sometimes part of other organ systems. There is not a privileged blood supply like there is to the brain and spinal cord, so peripheral nervous tissues do not need the same sort of protections. **40** The contraction of extraocular muscles is being tested, which is the function of the oculomotor, trochlear, and abducens nerves.

## Chapter 14

**1** Answers will vary, but a typical answer might be: I can eat most anything (except mushrooms!), so I don't think that I'm that sensitive to tastes. My whole family likes eating a variety of foods, so it seems that we all have the same level of sensitivity. **2** **Figure 14.9** The hair cells are located in the organ of Corti, which is located on the basilar membrane. The stereocilia of those cells would normally be attached to the tectorial membrane (though they are detached in the micrograph because of processing of the tissue). **3** The small bones in the middle ear, the ossicles, amplify and transfer sound between the tympanic membrane of the external ear and the oval window of the inner ear. **4** High frequencies activate hair cells toward the base of the cochlea, and low frequencies activate hair cells toward the apex of the cochlea. **5** Photoreceptors convert light energy, or photons, into an electrochemical signal. The retina contains bipolar cells and the RGCs that finally convert it into action potentials that are sent from the retina to the CNS. It is important to recognize when popular media and online sources oversimplify complex physiological processes so that misunderstandings are not generated. This video was created by a medical device manufacturer who might be trying to highlight other aspects of the visual system than retinal processing. The statement they make is not incorrect, it just bundles together several steps, which makes it sound like RGCs are the transducers, rather than photoreceptors. **6** Whereas the video shows opposite movement information in each eye for an object moving toward the face on the midline, movement past one side of the head will result in movement in the same direction on both retinae, but it will be slower in the eye on the side nearer to the object. **7** Even if a person cannot recognize a person's face, other cues such as clothing, hairstyle, or a particular feature such as a prominent nose or facial hair, can help make an identification. **8** The video only describes the lateral division of the corticospinal tract. The anterior division is omitted. **9** The movement disorders were similar to those seen in movement disorders

of the extrapyramidal system, which would mean the basal nuclei are the most likely source of haloperidol side effects. In fact, haloperidol affects dopamine activity, which is a prominent part of the chemistry of the basal nuclei. **10** The left eye also blinks. The sensory input from one eye activates the motor response of both eyes so that they both blink. **11** While walking, the sole of the foot may be scraped or scratched by many things. If the foot still reacted as in the Babinski reflex, an adult might lose their balance while walking. **12** B **13** D **14** B **15** D **16** C **17** C **18** D **19** A **20** A **21** B **22** D **23** B **24** A **25** C **26** A **27** The stevia molecule is similar to glucose such that it will bind to the glucose receptor in sweet-sensitive taste buds. However, it is not a substrate for the ATP-generating metabolism within cells. **28** The visual field for each eye is projected onto the retina as light is focused by the lens. The visual information from the right visual field falls on the left side of the retina and vice versa. The optic disc in the right eye is on the medial side of the fovea, which would be the left side of the retina. However, the optic disc in the left eye would be on the right side of that fovea, so the right visual field falls on the side of the retina in the left field where there is no blind spot. **29** The right leg would feel painful stimuli, but not touch, because the spinothalamic tract decussates at the level of entry, which would be below the injury, whereas the dorsal column system does not decussate until reaching the brain stem, which would be above the injury and thus those fibers would be damaged. **30** As the tumor enlarges, it would press against the optic chiasm, and fibers from the medial retina would be disrupted. These fibers carry information about the lateral visual field because the visual scene is reversed as the light passes through the pupil and lens. **31** The prefrontal cortex is involved in decision-making functions that lead to motor responses through connections to the more posterior motor regions. These early aspects of behavior are often associated with a person's personality, so disrupting those connections will lead to severe changes in behavior. **32** Though reflexes are simple circuits within the nervous system, they are representative of the more involved circuits of the somatic nervous system and can be used to quickly assess the state of neurological function for a person.

## Chapter 15

**1** The heart rate increases to send more blood to the muscles, and the liver releases stored glucose to fuel the muscles. **2** The endocrine system is also responsible for responses to stress in our lives. The hypothalamus coordinates the autonomic response through projections into the spinal cord and through influence over the pituitary gland, the effective center of the endocrine system. **3** The effect of gravity on circulation means that it is harder to get blood up from the legs as the body takes on a vertical orientation. **4** The optic nerve still carries the afferent input, but the output is from the thoracic spinal cord, through the superior cervical ganglion, to the radial fibers of the iris. **5** The release of urine in extreme fear. The sympathetic system normally constricts sphincters such as that of the urethra. **6** When the visual field is completely taken up by the movie, the brain is confused by the lack of vestibular stimuli to match the visual stimuli. Sitting to the side, or so that the edges of the screen can be seen, will help by providing a stable visual cue along with the magic of the cinematic experience. **7** D **8** A **9** C **10** B **11** A **12** C **13** D **14** B **15** A **16** C **17** A **18** C **19** B **20** D **21** B **22** A **23** C **24** C **25** D **26** B **27** Whereas energy is needed for running away from the threat, blood needs to be sent to the skeletal muscles for oxygen supply. The additional fuel, in the form of carbohydrates, probably wouldn't improve the ability to escape the threat as much as the diversion of oxygen-rich blood would hinder it. **28** The postganglionic sympathetic fiber releases norepinephrine, whereas the postganglionic parasympathetic fiber releases acetylcholine. Specific locations in the heart have adrenergic receptors and muscarinic receptors. Which receptors are bound is the signal that determines how the heart responds. **29** The nerves that carry sensory information from the diaphragm enter the spinal cord in the cervical region where somatic sensory fibers from the shoulder and neck would enter. The brain superimposes this experience onto the sensory homunculus where the somatic nerves are connected. **30** Within the cardiovascular system, different aspects demonstrate variation in autonomic tone. Heart rate is under parasympathetic tone, and blood pressure is under sympathetic tone. Pharmaceuticals that treat cardiovascular disorders may be more effective if they work with the normal state of the autonomic system. Alternatively, some disorders may be exacerbated by autonomic deficits and common therapies might not be as effective. **31** Pupillary dilation and sweating, two functions lost in Horner's syndrome, are caused by the sympathetic system. A tumor in the thoracic cavity may interrupt the output of the thoracic ganglia that project to the head and face. **32** The heart—based on the resting heart rate—is under parasympathetic tone, and the blood vessels—based on the lack of parasympathetic input—are under sympathetic tone. The vagus nerve contributes to the lowered resting heart rate, whereas the vasomotor nerves maintain the slight constriction of systemic blood vessels. **33** Blood vessels, and therefore blood pressure, are primarily influenced by only the sympathetic system. There is no parasympathetic influence on blood pressure, so nicotine activation of autonomic ganglia will preferentially increase blood pressure. Also, cardiac muscle tissue is only modulated by autonomic inputs, so the conflicting information from both sympathetic and parasympathetic postganglionic fibers will cause arrhythmias. Both hypertension and arrhythmias are cardiac risk factors. **34** Drops of these substances into the eyes, as was once done cosmetically, blocks the muscarinic receptors in the smooth muscle of the iris. The concentration of this direct application is probably below the concentration that would cause poisoning if it got into the bloodstream. The possibility of that concentration being wrong and causing poisoning is too great, however, for atropine to be used as a cosmetic.

## Chapter 16

**1** Coordination and gait were tested first, followed by mental status, motor, sensory, and reflexes. There were no specific tests of the cranial nerves. **2** History is the report from the patient, or others familiar with the patient, that can assist in diagnosis and formulation of treatment and care—essentially the result of an interview with the patient. **3** The patient was unable to form episodic memories during the events described in the case, so the medial temporal lobe structures might have been affected by the antibodies. **4** The left hemisphere of the cerebrum controls the right side of the body through the corticospinal tract. Because language function is largely associated with the dominant hemisphere, the hand with which a person writes will most likely be the one controlled by the left hemisphere. **5** She has just demonstrated voluntary control by closing her eyes, but when he provides the resistance that she needs to hold tight against, she has already relaxed the muscles enough for him to pull them open. She needs

to squeeze them tighter to demonstrate the strength she has in the orbicular oculi. **6** The fingertips are the most sensitive skin on the hand, so the points of the caliper can be closer together and still be recognized as two separate points. On the palm, the sensitivity is less, so the points need to be farther apart. This will continue on the arm and shoulder, as sensitivity decreases, the discrimination of separate stimuli will be wider. **7** The region lateral to the umbilicus is innervated by T9–T11, approximately. A lack of contraction following that stimulation would therefore suggest damage at those levels. **8** A wide stance would suggest the person needs to maintain balance by broadening their base. Instead of continuous correction to posture, this can keep the body stable when the cerebellum cannot. **9** D **10** A **11** C **12** B **13** D **14** C **15** D **16** B **17** A **18** C **19** A **20** A **21** D **22** A **23** C **24** A **25** D **26** B **27** C **28** D **29** C **30** A **31** B **32** C **33** D **34** If an ischemic event has occurred, nervous tissue may be compromised, but quick intervention—possibly within a few hours—may be the critical aspect of recovery. **35** The main difference between a stroke and TIA is time. If the result of a cerebrovascular accident lasts longer than 24 hours, then it is considered a stroke. Otherwise, it is considered transient and is labeled a TIA. **36** The patient has suffered a stroke to the prefrontal cortex where working memory is localized. **37** Wernicke's area is associated with the comprehension of language, so the person probably doesn't understand the question being asked and cannot respond meaningfully. This is called a receptive aphasia. **38** If the person already has problems focusing on far objects, and wears corrective lenses to see farther objects, then as accommodation changes, focusing on a reading surface might still be in their naturally near-sighted range. **39** The medulla is where the accessory nerve, which controls the sternocleidomastoid muscle, and the hypoglossal nerve, which controls the genioglossus muscle, are both located. The weakness of the left side of the neck, and the tendency of the tongue to point to that side, both show that the damage is on the left side of the brain stem. **40** Where spinal nerves innervate the skin is represented by "slices" of the body surface referred to as dermatomes. The fibers originating in each region are contained within the same spinal nerve, which relates to the perception of that localization. **41** Paralysis means that voluntary muscle control is not possible because of the interruption of descending motor input. Spasticity refers to what could be called "hypercontractility" of the muscles in the absence of the descending input. **42** The spinocerebellum is related to controlling the axial muscles and keeps the body balanced on the bike. The cerebrocerebellum is related to controlling the appendicular muscles and keeps the legs moving to pedal the bike. The vestibulocerebellum receives input about equilibrium to help keep everything balanced as the bike is moving forward. **43** Rapid alternating movements in speech relate to how the lips, tongue, and palate move to produce speech sounds. The cerebrocerebellum is required for the proper implementation of these movements.

## Chapter 17

**1** cAMP **2** Thyroid-stimulating hormone. **3** Cortisol. **4** Turning on the lights. **5** Insulin is overproduced. **6** C **7** B **8** B **9** B **10** C **11** B **12** C **13** A **14** B **15** D **16** B **17** C **18** C **19** D **20** B **21** C **22** A **23** B **24** D **25** B **26** B **27** C **28** D **29** A **30** D **31**B **32** B **33** D **34** C **35** A **36** A **37** B **38** The endocrine system uses chemical signals called hormones to convey information from one part of the body to a distant part of the body. Hormones are released from the endocrine cell into the extracellular environment, but then travel in the bloodstream to target tissues. This communication and response can take seconds to days. In contrast, neurons transmit electrical signals along their axons. At the axon terminal, the electrical signal prompts the release of a chemical signal called a neurotransmitter that carries the message across the synaptic cleft to elicit a response in the neighboring cell. This method of communication is nearly instantaneous, of very brief duration, and is highly specific. **39** Endocrine glands are ductless. They release their secretion into the surrounding fluid, from which it enters the bloodstream or lymph to travel to distant cells. Moreover, the secretions of endocrine glands are hormones. Exocrine glands release their secretions through a duct that delivers the secretion to the target location. Moreover, the secretions of exocrine glands are not hormones, but compounds that have an immediate physiologic function. For example, pancreatic juice contains enzymes that help digest food. **40** True. Neurotransmitters can be classified as paracrines because, upon their release from a neuron's axon terminals, they travel across a microscopically small cleft to exert their effect on a nearby neuron or muscle cell. **41** In both cAMP and $IP_3$–calcium signaling, a hormone binds to a cell membrane hormone receptor that is coupled to a G protein. The G protein becomes activated when the hormone binds. In the case of cAMP signaling, the activated G protein activates adenylyl cyclase, which causes ATP to be converted to cAMP. This second messenger can then initiate other signaling events, such as a phosphorylation cascade. In the case of $IP_3$–calcium signaling, the activated G protein activates phospholipase C, which cleaves a membrane phospholipid compound into DAG and $IP_3$. $IP_3$ causes the release of calcium, another second messenger, from intracellular stores. This causes further signaling events. **42** An intracellular hormone receptor is located within the cell. A hydrophobic hormone diffuses through the cell membrane and binds to the intracellular hormone receptor, which may be in the cytosol or in the cell nucleus. This hormone–receptor complex binds to a segment of DNA. This initiates the transcription of a target gene, the end result of which is protein assembly and the hormonal response. **43** The anterior lobe of the pituitary gland is connected to the hypothalamus by vasculature, which allows regulating hormones from the hypothalamus to travel to the anterior pituitary. In contrast, the posterior lobe is connected to the hypothalamus by a bridge of nerve axons called the hypothalamic–hypophyseal tract, along which the hypothalamus sends hormones produced by hypothalamic nerve cell bodies to the posterior pituitary for storage and release into the circulation. **44** The mammary glands are the target tissues for prolactin. **45** Iodine deficiency in a pregnant woman would also deprive the fetus. Iodine is required for the synthesis of thyroid hormones, which contribute to fetal growth and development, including maturation of the nervous system. Insufficient amounts would impair these functions. **46** Hyperthyroidism is an abnormally elevated blood level of thyroid hormones due to an overproduction of $T_3$ and $T_4$. An individual with hyperthyroidism is likely to lose weight because one of the primary roles of thyroid hormones is to increase the body's basal metabolic rate, increasing the breakdown of nutrients and the production of ATP. **47** The production and secretion of PTH is regulated by a negative feedback loop. Low blood calcium levels initiate the production and secretion of PTH. PTH increases bone resorption, calcium absorption from the intestines, and calcium reabsorption by the kidneys. As a result, blood calcium levels begin to rise. This, in turn, inhibits the further production and secretion of PTH. **48** A parathyroid gland tumor can prompt hypersecretion of PTH. This can raise blood calcium levels so excessively that calcium deposits begin to

accumulate throughout the body, including in the kidney tubules, where they are referred to as kidney stones. **49** The outer region is the zona glomerulosa, which produces mineralocorticoids such as aldosterone; the next region is the zona fasciculata, which produces glucocorticoids such as cortisol; the inner region is the zona reticularis, which produces androgens. **50** Damage to the innervation of the adrenal medulla would prevent the adrenal glands from responding to the hypothalamus during the fight-or-flight response. Therefore, the response would be reduced. **51** The short-term stress response involves the hormones epinephrine and norepinephrine, which work to increase the oxygen supply to organs important for extreme muscular action such as the brain, lungs, and muscles. In the long-term stress response, the hormone cortisol is involved in catabolism of glycogen stores, proteins, and triglycerides, glucose and ketone synthesis, and downregulation of the immune system. **52** SAD is thought to occur in part because low levels and duration of sunlight allow excessive and prolonged secretion of melatonin. Light therapy—daytime exposure to very bright lighting—is one common therapy. **53** The retina is important for melatonin production because it senses light. Bright light inhibits the production of melatonin, whereas low light levels promote the production of melatonin. Therefore, deterioration of the retinas would most likely disturb the sleep-wake pattern because melatonin production would be elevated. **54** Both estrogens and progesterone are steroid hormones produced by the ovaries that help regulate the menstrual cycle. Estrogens play an important role in the development of the female reproductive tract and secondary sex characteristics. They also help maintain pregnancy. Progesterone prepares the body for pregnancy and helps maintain pregnancy. **55** Relaxin produced by the placenta is thought to soften and widen the pubic symphysis. This increases the size of the pelvic outlet, the birth canal through which the fetus passes during vaginal childbirth. **56** The beta cells produce the hormone insulin, which is important in the regulation of blood glucose levels. All insulin-dependent cells of the body require insulin in order to take up glucose from the bloodstream. Destruction of the beta cells would result in an inability to produce and secrete insulin, leading to abnormally high blood glucose levels and the disease called type 1 diabetes mellitus. **57** Excessive blood glucose levels damage the blood vessels and nerves of the body's extremities, increasing the risk for injury, infection, and tissue death. Loss of sensation to the feet means that a diabetic patient will not be able to feel foot trauma, such as from ill-fitting shoes. Even minor injuries commonly lead to infection, which , can progress to tissue death without proper care, requiring amputation. **58** The presence of food in the GI tract stimulates the release of hormones that aid in digestion. For example, gastrin is secreted in response to stomach distention and causes the release of hydrochloric acid in the stomach. Secretin is secreted when acidic chyme enters the small intestine, and stimulates the release of pancreatic bicarbonate. In the presence of fat and protein in the duodenum, CCK stimulates the release of pancreatic digestive enzymes and bile from the gallbladder. Other GI tract hormones aid in glucose metabolism and other functions. **59** The thymus gland is important for the development and maturation of T cells. During infancy and early childhood, the thymus gland is large and very active, as the immune system is still developing. During adulthood, the thymus gland atrophies because the immune system is already developed. **60** Menopause occurs as the result of a progressive decline in the function of the ovaries, resulting in low estrogen and progesterone levels. Ovulation ceases, and postmenopausal woman can no longer conceive a child. In contrast, andropause is a much more gradual and subtle decline in testosterone levels and functioning. A man typically maintains fertility until very old age, although the quantity, quality, and motility of the sperm he produces may be reduced.

## Chapter 18

**1** There are values given for percent saturation, tension, and blood gas, and there are listings for different types of hemoglobin. **2** Side effects can include heart disease, stroke, pulmonary embolism, and virus transmission. **3** **Figure 18.13** This should appear to be a normal blood smear. **4** Clotting factors flow through the blood vessels in their inactive state. The endothelium does not have thrombogenic tissue factor to activate clotting factors. **5** C **6** B **7** D **8** C **9** A **10** D **11** A **12** C **13** D **14** C **15** D **16** C **17** B **18** B **19** A **20** D **21** A **22** C **23** B **24** C **25** B **26** D **27** The patient's blood is approximately 58 percent plasma (since the buffy coat is less than 1 percent). **28** The formed elements include erythrocytes and leukocytes, which are cells (although mature erythrocytes do not have a nucleus); however, the formed elements also include platelets, which are not true cells but cell fragments. **29** False. The buffy coat is the portion of blood that is made up of its leukocytes and platelets. **30** When disease impairs the ability of the bone marrow to participate in hemopoiesis, extramedullary hemopoiesis begins in the patient's liver and spleen. This causes the spleen to enlarge. **31** The adjective myelogenous suggests a condition originating from (generated by) myeloid cells. Acute myelogenous leukemia impairs the production of erythrocytes and other mature formed elements of the myeloid stem cell lineage. Lymphocytes arise from the lymphoid stem cell line. **32** She is at risk for anemia, because her unusually heavy menstrual bleeding results in excessive loss of erythrocytes each month. At the same time, her vegan diet means that she does not have dietary sources of heme iron. The non-heme iron she consumes in plant foods is not as well absorbed as heme iron. **33** Bilirubin is a breakdown product of the non-iron component of heme, which is cleaved from globin when erythrocytes are degraded. Excessive erythrocyte destruction would deposit excessive bilirubin in the blood. Bilirubin is a yellowish pigment, and high blood levels can manifest as yellowed skin. **34** A neutrophil count below 1800 cells per microliter is considered abnormal. Thus, this patient's ANC is at the low end of the normal range and there would be no reason to delay chemotherapy. In clinical practice, most patients are given chemotherapy if their ANC is above 1000. **35** Any severe stress can increase the leukocyte count, resulting in leukocytosis. A burn is especially likely to increase the proliferation of leukocytes in order to ward off infection, a significant risk when the barrier function of the skin is destroyed. **36** When blood contacts glass, the extrinsic coagulation pathway is initiated. This leads to the common pathway, and the blood clots. Within about 30 minutes, the clot begins to shrink. After an hour, it is about half its original size. Its heavier weight will cause it to fall to the bottom of the tube during centrifugation, allowing the lab technician to harvest the serum remaining at the top. **37** In a thrombotic stroke, a blood vessel to the brain has been blocked by a thrombus, an aggregation of platelets and erythrocytes within a blood vessel. A thrombolytic agent is a medication that promotes the breakup of thrombi. **38** In emergency situations, blood type $O^-$ will be infused until cross matching can be done. Blood type $O^-$ is called the universal donor blood because the erythrocytes have neither A nor B antigens on their surface, and the Rh factor is negative. **39** The lab technician has not made an error. Blood type AB has both A and B surface antigens, and neither anti-A nor anti-B antibodies circulating in the plasma. When anti-A antibodies (added to the first well) contact A antigens

on AB erythrocytes, they will cause agglutination. Similarly, when anti-B antibodies contact B antigens on AB erythrocytes, they will cause agglutination.

## Chapter 19

**1** The pressure gradient between the atria and the ventricles is much greater than that between the ventricles and the pulmonary trunk and aorta. Without the presence of the chordae tendineae and papillary muscles, the valves would be blown back (prolapsed) into the atria and blood would regurgitate. **2** D **3** A **4** A **5** C **6** B **7** B **8** C **9** C **10** D **11** D **12** D **13** D **14** B **15** C **16** B **17** B **18** A **19** B **20** B **21** C **22** D **23** C **24** D **25** A **26** D **27** When the ventricles contract and pressure begins to rise in the ventricles, there is an initial tendency for blood to flow back (regurgitate) to the atria. However, the papillary muscles also contract, placing tension on the chordae tendineae and holding the atrioventricular valves (tricuspid and mitral) in place to prevent the valves from prolapsing and being forced back into the atria. The semilunar valves (pulmonary and aortic) lack chordae tendineae and papillary muscles, but do not face the same pressure gradients as do the atrioventricular valves. As the ventricles relax and pressure drops within the ventricles, there is a tendency for the blood to flow backward. However, the valves, consisting of reinforced endothelium and connective tissue, fill with blood and seal off the opening preventing the return of blood. **28** The pulmonary circuit consists of blood flowing to and from the lungs, whereas the systemic circuit carries blood to and from the entire body. The systemic circuit is far more extensive, consisting of far more vessels and offers much greater resistance to the flow of blood, so the heart must generate a higher pressure to overcome this resistance. This can be seen in the thickness of the myocardium in the ventricles. **29** It prevents additional impulses from spreading through the heart prematurely, thereby allowing the muscle sufficient time to contract and pump blood effectively. **30** It ensures sufficient time for the atrial muscle to contract and pump blood into the ventricles prior to the impulse being conducted into the lower chambers. **31** Gap junctions within the intercalated disks allow impulses to spread from one cardiac muscle cell to another, allowing sodium, potassium, and calcium ions to flow between adjacent cells, propagating the action potential, and ensuring coordinated contractions. **32** Without a true resting potential, there is a slow influx of sodium ions through slow channels that produces a prepotential that gradually reaches threshold. **33** The cardiac cycle comprises a complete relaxation and contraction of both the atria and ventricles, and lasts approximately 0.8 seconds. Beginning with all chambers in diastole, blood flows passively from the veins into the atria and past the atrioventricular valves into the ventricles. The atria begin to contract following depolarization of the atria and pump blood into the ventricles. The ventricles begin to contract, raising pressure within the ventricles. When ventricular pressure rises above the pressure in the two major arteries, blood pushes open the two semilunar valves and moves into the pulmonary trunk and aorta in the ventricular ejection phase. Following ventricular repolarization, the ventricles begin to relax, and pressure within the ventricles drops. When the pressure falls below that of the atria, blood moves from the atria into the ventricles, opening the atrioventricular valves and marking one complete heart cycle. **34** Increasing EDV increases the sarcomeres' lengths within the cardiac muscle cells, allowing more cross bridge formation between the myosin and actin and providing for a more powerful contraction. This relationship is described in the Frank-Starling mechanism. **35** Afterload represents the resistance within the arteries to the flow of blood ejected from the ventricles. If uncompensated, if afterload increases, flow will decrease. In order for the heart to maintain adequate flow to overcome increasing afterload, it must pump more forcefully. This is one of the negative consequences of high blood pressure or hypertension. **36** The human embryo is rapidly growing and has great demands for nutrients and oxygen, while producing waste products including carbon dioxide. All of these materials must be received from or delivered to the mother for processing. Without an efficient early circulatory system, this would be impossible. **37** After fusion of the two endocardial tubes into the single primitive heart, five regions quickly become visible. From the head, these are the truncus arteriosus, bulbus cordis, primitive ventricle, primitive atrium, and sinus venosus. Contractions propel the blood from the sinus venosus to the truncus arteriosus. About day 23, the heart begins to form an S-shaped structure within the pericardium. The bulbus cordis develops into the right ventricle, whereas the primitive ventricle becomes the left ventricle. The interventricular septum separating these begins to form about day 28. The atrioventricular valves form between weeks five to eight. At this point, the heart ventricles resemble the adult structure.

## Chapter 20

**1** Water. **2** Take medications as prescribed, eat a healthy diet, exercise, and don't smoke. **3** A **4** D **5** C **6** B **7** C **8** B **9** A **10** B **11** D **12** D **13** B **14** D **15** A **16** D **17** C **18** C **19** A **20** B **21** C **22** C **23** D **24** A **25** D **26** B **27** C **28** Arterioles receive blood from arteries, which are vessels with a much larger lumen. As their own lumen averages just 30 micrometers or less, arterioles are critical in slowing down—or resisting—blood flow. The arterioles can also constrict or dilate, which varies their resistance, to help distribute blood flow to the tissues. **29** Vasoconstriction causes the lumens of blood vessels to narrow. This increases the pressure of the blood flowing within the vessel. **30** This is a venule. **31** The patient's pulse pressure is 130 – 85 = 45 mm Hg. Generally, a pulse pressure should be at least 25 percent of the systolic pressure, but not more than 100 mm Hg. Since 25 percent of 130 = 32.5, the patient's pulse pressure of 45 is normal. The patient's mean arterial pressure is 85 + 1/3 (45) = 85 + 15 = 100. Normally, the mean arterial blood pressure falls within the range of 70 – 110 mmHg, so 100 is normal. **32** People who stand upright all day and are inactive overall have very little skeletal muscle activity in the legs. Pooling of blood in the legs and feet is common. Venous return to the heart is reduced, a condition that in turn reduces cardiac output and therefore oxygenation of tissues throughout the body. This could at least partially account for the patient's fatigue and shortness of breath, as well as her "spaced out" feeling, which commonly reflects reduced oxygen to the brain. **33** The patient's blood would flow more sluggishly from the arteriole into the capillary bed. Thus, the patient's capillary hydrostatic pressure would be below the normal 35 mm Hg at the arterial end. At the same time, the patient's blood colloidal osmotic pressure is normal—about 25 mm Hg. Thus, even at the arterial end of the capillary bed, the net filtration pressure would be below 10 mm Hg, and an abnormally reduced level of filtration would occur. In fact, reabsorption might begin to occur by the midpoint of the capillary bed. **34** False. The plasma proteins suspended

in blood cannot cross the semipermeable capillary cell membrane, and so they remain in the plasma within the vessel, where they account for the blood colloid osmotic pressure. **35** This blood pressure is insufficient to circulate blood throughout the patient's body and maintain adequate perfusion of the patient's tissues. Ischemia would prompt hypoxia, including to the brain, prompting confusion. The low blood pressure would also trigger the renin-angiotensin-aldosterone mechanism, and release of aldosterone would stimulate the thirst mechanism in the hypothalamus. **36** Nitric oxide is a very powerful local vasodilator that is important in the autoregulation of tissue perfusion. If it were not broken down very quickly after its release, blood flow to the region could exceed metabolic needs. **37** The right ventricle of the heart pumps oxygen-depleted blood to the pulmonary arteries. **38** The gonadal veins drain the testes in males and the ovaries in females. **39** The internal carotid arteries and the vertebral arteries provide most of the brain's blood supply. **40** Angiogenesis inhibitors are drugs that inhibit the growth of new blood vessels. They can impede the growth of tumors by limiting their blood supply and therefore their access to gas and nutrient exchange. **41** The ductus arteriosus is a blood vessel that provides a passageway between the pulmonary trunk and the aorta during fetal life. Most blood ejected from the fetus' right ventricle and entering the pulmonary trunk is diverted through this structure into the fetal aorta, thus bypassing the fetal lungs.

## Chapter 21

**1** The three main components are the lymph vessels, the lymph nodes, and the lymph. **2** The dendritic cell transports the virus to a lymph node. **3** The bacterium is digested by the phagocyte's digestive enzymes (contained in its lysosomes). **4** Breastfeeding is an example of natural immunity acquired passively. **5** B **6** A **7** C **8** D **9** A **10** C **11** D **12** B **13** C **14** B **15** B **16** D **17** B **18** C **19** D **20** D **21** D **22** A **23** B **24** D **25** C **26** B **27** B **28** A **29** C **30** C **31** D **32** C **33** A **34** B **35** B **36** A **37** B **38** D **39** The lymph enters through lymphatic capillaries, and then into larger lymphatic vessels. The lymph can only go in one direction due to valves in the vessels. The larger lymphatics merge to form trunks that enter into the blood via lymphatic ducts. **40** The cell debris and damaged cells induce macrophages to begin to clean them up. Macrophages release cytokines that attract neutrophils, followed by more macrophages. Other mediators released by mast cells increase blood flow to the area and also vascular permeability, allowing the recruited cells to get from the blood to the site of infection, where they can phagocytose the dead cells and debris, preparing the site for wound repair. **41** Interferons are produced in virally infected cells and cause them to secrete signals for surrounding cells to make antiviral proteins. C-reactive protein is induced to be made by the liver and will opsonize certain species of bacteria. **42** The antigen is digested by the proteasome, brought into the endoplasmic reticulum by the TAP transporter system, where it binds to class I MHC molecules. These are taken to the cell surface by transport vesicles. **43** Antigen-specific clones are stimulated as their antigen receptor binds to antigen. They are then activated and proliferate, expanding their numbers. The result is a large number of antigen-specific lymphocytes. **44** B cells activated during a primary response differentiate either into terminally differentiated plasma cells or into memory B cells. These memory B cells are what respond during a secondary or memory antibody response. **45** IgM is an antigen receptor on naïve B cells. Upon activation, naïve B cells make IgM first. IgM is good at binding complement and thus has good antibacterial effects. IgM is replaced with other classes of antibodies later on in the primary response due to class switching. **46** Seroconversion is the clearance of virus in the serum due to the increase in specific serum antibody levels. Seroconversion happens in the early stages of HIV disease. Unfortunately, the antibody cannot completely clear the virus from the body and thus it most often progresses to AIDS. **47** Tuberculosis is caused by bacteria resistant to lysosomal enzymes in alveolar macrophages, resulting in chronic infection. The immune response to these bacteria actually causes most of the lung damage that is characteristic of this life-threatening disease. **48** The peanuts cause high levels of mast cell degranulation in the throats of these individuals. The histamine released increases vascular permeability, causing edema and (swelling), making breathing difficult. This must be treated with epinephrine as soon as possible. **49** Antibody response to the cell walls of β-*Streptococcus* cross-reacts with the heart muscle. Complement is then activated and the heart is damaged, leading to abnormal function. Tolerance is broken because heart myosin antigens are similar to antigens on the β-*Streptococcus* bacteria. **50** Stress causes the release of hormones and the activation of nerves that suppress the immune response. Short-term stress has little effect on the health of an already healthy individual, whereas chronic stress does lead to increases in disease in such people.

## Chapter 22

**1** Inflammation and the production of a thick mucus; constriction of the airway muscles, or bronchospasm; and an increased sensitivity to allergens. **2** Patients with respiratory ailments (such as asthma, emphysema, COPD, etc.) have issues with airway resistance and/or lung compliance. Both of these factors can interfere with the patient's ability to move air effectively. A spirometry test can determine how much air the patient can move into and out of the lungs. If the air volumes are low, this can indicate that the patient has a respiratory disease or that the treatment regimen may need to be adjusted. If the numbers are normal, the patient does not have a significant respiratory disease or the treatment regimen is working as expected. **3** When oxygen binds to the hemoglobin molecule, oxyhemoglobin is created, which has a red color to it. Hemoglobin that is not bound to oxygen tends to be more of a blue–purple color. Oxygenated blood traveling through the systemic arteries has large amounts of oxyhemoglobin. As blood passes through the tissues, much of the oxygen is released into systemic capillaries. The deoxygenated blood returning through the systemic veins, therefore, contains much smaller amounts of oxyhemoglobin. The more oxyhemoglobin that is present in the blood, the redder the fluid will be. As a result, oxygenated blood will be much redder in color than deoxygenated blood. **4** C **5** A **6** D **7** A **8** C **9** C **10** B **11** A **12** C **13** A **14** A **15** C **16** D **17** A **18** D **19** A **20** D **21** A **22** C **23** B **24** C **25** D **26** B **27** A **28** A **29** D **30** D **31** C **32** A **33** B **34** A **35** C **36** The pharynx has three major regions. The first region is the nasopharynx, which is connected to the posterior nasal cavity and functions as an airway. The second region is the oropharynx, which is continuous with the nasopharynx and is connected to the oral cavity at the fauces. The laryngopharynx is connected to the oropharynx and the esophagus and trachea. Both the oropharynx and laryngopharynx are passageways for air and food and

drink. **37** The epiglottis is a region of the larynx that is important during the swallowing of food or drink. As a person swallows, the pharynx moves upward and the epiglottis closes over the trachea, preventing food or drink from entering the trachea. If a person's epiglottis were injured, this mechanism would be impaired. As a result, the person may have problems with food or drink entering the trachea, and possibly, the lungs. Over time, this may cause infections such as pneumonia to set in. **38** The conducting zone of the respiratory system includes the organs and structures that are not directly involved in gas exchange, but perform other duties such as providing a passageway for air, trapping and removing debris and pathogens, and warming and humidifying incoming air. Such structures include the nasal cavity, pharynx, larynx, trachea, and most of the bronchial tree. The respiratory zone includes all the organs and structures that are directly involved in gas exchange, including the respiratory bronchioles, alveolar ducts, and alveoli. **39** The right and left lungs differ in size and shape to accommodate other organs that encroach on the thoracic region. The right lung consists of three lobes and is shorter than the left lung, due to the position of the liver underneath it. The left lung consist of two lobes and is longer and narrower than the right lung. The left lung has a concave region on the mediastinal surface called the cardiac notch that allows space for the heart. **40** There is a cavity, called the pleural cavity, between the parietal and visceral layers of the pleura. Mesothelial cells produce and secrete pleural fluid into the pleural cavity that acts as a lubricant. Therefore, as you breathe, the pleural fluid prevents the two layers of the pleura from rubbing against each other and causing damage due to friction. **41** Lung compliance refers to the ability of lung tissue to stretch under pressure, which is determined in part by the surface tension of the alveoli and the ability of the connective tissue to stretch. Lung compliance plays a role in determining how much the lungs can change in volume, which in turn helps to determine pressure and air movement. **42** Quiet breathing occurs at rest and without active thought. During quiet breathing, the diaphragm and external intercostal muscles work at different extents, depending on the situation. For inspiration, the diaphragm contracts, causing the diaphragm to flatten and drop towards the abdominal cavity, helping to expand the thoracic cavity. The external intercostal muscles contract as well, causing the rib cage to expand, and the rib cage and sternum to move outward, also expanding the thoracic cavity. Expansion of the thoracic cavity also causes the lungs to expand, due to the adhesiveness of the pleural fluid. As a result, the pressure within the lungs drops below that of the atmosphere, causing air to rush into the lungs. In contrast, expiration is a passive process. As the diaphragm and intercostal muscles relax, the lungs and thoracic tissues recoil, and the volume of the lungs decreases. This causes the pressure within the lungs to increase above that of the atmosphere, causing air to leave the lungs. **43** Respiratory rate is defined as the number of breaths taken per minute. Respiratory rate is controlled by the respiratory center, located in the medulla oblongata. Conscious thought can alter the normal respiratory rate through control by skeletal muscle, although one cannot consciously stop the rate altogether. A typical resting respiratory rate is about 14 breaths per minute. **44** Both Dalton's and Henry's laws describe the behavior of gases. Dalton's law states that any gas in a mixture of gases exerts force as if it were not in a mixture. Henry's law states that gas molecules dissolve in a liquid proportional to their partial pressure. **45** The damaged alveoli will have insufficient ventilation, causing the partial pressure of oxygen in the alveoli to decrease. As a result, the pulmonary capillaries serving these alveoli will constrict, redirecting blood flow to other alveoli that are receiving sufficient ventilation. **46** Both adult and fetal hemoglobin transport oxygen via iron molecules. However, fetal hemoglobin has about a 20-fold greater affinity for oxygen than does adult hemoglobin. This is due to a difference in structure; fetal hemoglobin has two subunits that have a slightly different structure than the subunits of adult hemoglobin. **47** The relationship between the partial pressure of oxygen and the binding of hemoglobin to oxygen is described by the oxygen–hemoglobin saturation/dissociation curve. As the partial pressure of oxygen increases, the number of oxygen molecules bound by hemoglobin increases, thereby increasing the saturation of hemoglobin. **48** Carbon dioxide can be transported by three mechanisms: dissolved in plasma, as bicarbonate, or as carbaminohemoglobin. Dissolved in plasma, carbon dioxide molecules simply diffuse into the blood from the tissues. Bicarbonate is created by a chemical reaction that occurs mostly in erythrocytes, joining carbon dioxide and water by carbonic anhydrase, producing carbonic acid, which breaks down into bicarbonate and hydrogen ions. Carbaminohemoglobin is the bound form of hemoglobin and carbon dioxide. **49** There are three neural factors that play a role in the increased ventilation observed during exercise. Because this increased ventilation occurs at the beginning of exercise, it is unlikely that only blood oxygen and carbon dioxide levels are involved. The first neural factor is the psychological stimulus of making a conscious decision to exercise. The second neural factor is the stimulus of motor neuron activation by the skeletal muscles, which are involved in exercise. The third neural factor is activation of the proprioceptors located in the muscles, joints, and tendons that stimulate activity in the respiratory centers. **50** A major mechanism involved in acclimatization is the increased production of erythrocytes. A drop in tissue levels of oxygen stimulates the kidneys to produce the hormone erythropoietin, which signals the bone marrow to produce erythrocytes. As a result, individuals exposed to a high altitude for long periods of time have a greater number of circulating erythrocytes than do individuals at lower altitudes. **51** At about week 28, enough alveolar precursors have matured so that a baby born prematurely at this time can usually breathe on its own. Other structures that develop about this time are pulmonary capillaries, expanding to create a large surface area for gas exchange. Alveolar ducts and alveolar precursors have also developed. **52** Fetal breathing movements occur due to the contraction of respiratory muscles, causing the fetus to inhale and exhale amniotic fluid. It is thought that these movements are a way to "practice" breathing, which results in toning the muscles in preparation for breathing after birth. In addition, fetal breathing movements may help alveoli to form and mature.

## Chapter 23

**1** Answers may vary. **2** Answers may vary. **3** Answers may vary. **4** Answers may vary. **5** Answers may vary. **6** Answers may vary. **7** Answers may vary. **8** A **9** A **10** D **11** D **12** B **13** D **14** A **15** C **16** B **17** A **18** D **19** C **20** A **21** D **22** B **23** B **24** B **25** D **26** A **27** D **28** C **29** A **30** B **31** D **32** B **33** The enteric nervous system helps regulate alimentary canal motility and the secretion of digestive juices, thus facilitating digestion. If a person becomes overly anxious, sympathetic innervation of the alimentary canal is stimulated, which can result in a slowing of digestive activity. **34** The lamina propria of the mucosa contains lymphoid tissue that makes up the MALT and responds to pathogens encountered in the alimentary canal. **35** The majority of digestion and absorption occurs in the small intestine. By slowing the transit of chyme, segmentation and a reduced rate of peristalsis allow time for these processes to occur. **36** The smell of food initiates long reflexes, which result

in the secretion of digestive juices. **37** Parotid gland saliva is watery with little mucus but a lot of amylase, which allows it to mix freely with food during mastication and begin the digestion of carbohydrates. In contrast, sublingual gland saliva has a lot of mucus with the least amount of amylase of all the salivary glands. The high mucus content serves to lubricate the food for swallowing. **38** The incisors. Since these teeth are used for tearing off pieces of food during ingestion, the player will need to ingest foods that have already been cut into bite-sized pieces until the broken teeth are replaced. **39** Usually when food is swallowed, involuntary muscle contractions cause the soft palate to rise and close off the nasopharynx. The larynx also is pulled up, and the epiglottis folds over the glottis. These actions block off the air passages. **40** If the lower esophageal sphincter does not close completely, the stomach's acidic contents can back up into the esophagus, a phenomenon known as GERD. **41** Peristalsis moves the bolus down the esophagus and toward the stomach. Esophageal glands secrete mucus that lubricates the bolus and reduces friction. When the bolus nears the stomach, the lower esophageal sphincter relaxes, allowing the bolus to pass into the stomach. **42** The mucosal barrier protects the stomach from self-digestion. It includes a thick coating of bicarbonate-rich mucus; the mucus is physically protective, and bicarbonate neutralizes gastric acid. Epithelial cells meet at tight junctions, which block gastric juice from penetrating the underlying tissue layers, and stem cells quickly replace sloughed off epithelial mucosal cells. **43** The stomach has an additional inner oblique smooth muscle layer that helps the muscularis churn and mix food. The epithelium includes gastric glands that secrete gastric fluid. The gastric fluid consists mainly of mucous, HCl, and the enzyme pepsin released as pepsinogen. **44** Nutrients from the breakdown of carbohydrates and proteins are absorbed through a capillary bed in the villi of the small intestine. Lipid breakdown products are absorbed into a lacteal in the villi, and transported via the lymphatic system to the bloodstream. **45** If large quantities of chyme were forced into the small intestine, it would result in osmotic water loss from the blood into the intestinal lumen that could cause potentially life-threatening low blood volume and erosion of the duodenum. **46** The mucosa of the small intestine includes circular folds, villi, and microvilli. The wall of the large intestine has a thick mucosal layer, and deeper and more abundant mucus-secreting glands that facilitate the smooth passage of feces. There are three features that are unique to the large intestine: teniae coli, haustra, and epiploic appendages. **47** The pancreas secretes protein-digesting enzymes in their inactive forms. If secreted in their active forms, they would self-digest the pancreas. These enzymes are activated in the duodenum. **48** The hepatocytes are the main cell type of the liver. They process, store, and release nutrients into the blood. Radiating out from the central vein, they are tightly packed around the hepatic sinusoids, allowing the hepatocytes easy access to the blood flowing through the sinusoids. **49** Bile salts and lecithin can emulsify large lipid globules because they are amphipathic; they have a nonpolar (hydrophobic) region that attaches to the large fat molecules as well as a polar (hydrophilic) region that interacts with the watery chime in the intestine. **50** Intrinsic factor secreted in the stomach binds to the large $B_{12}$ compound, creating a combination that can bind to mucosal receptors in the ileum.

## Chapter 24

**1** C **2** B **3** A **4** B **5** C **6** B **7** C **8** D **9** A **10** D **11** D **12** A **13** C **14** B **15** C **16** D **17** A **18** B **19** D **20** A **21** C **22** B **23** D **24** A **25** C **26** C **27** A **28** C **29** B **30** An increase or decrease in lean muscle mass will result in an increase or decrease in metabolism. **31** Addison's disease is characterized by low cortisol levels. One way to treat the disease is by giving cortisol to the patient. **32** Glucose is oxidized during glycolysis, creating pyruvate, which is processed through the Krebs cycle to produce NADH, $FADH_2$, ATP, and $CO_2$. The $FADH_2$ and NADH yield ATP. **33** Upon entry into the cell, hexokinase or glucokinase phosphorylates glucose, converting it into glucose-6-phosphate. In this form, glucose-6-phosphate is trapped in the cell. Because all of the glucose has been phosphorylated, new glucose molecules can be transported into the cell according to its concentration gradient. **34** Carbohydrates are converted into pyruvate during glycolysis. This pyruvate is converted into acetyl CoA and proceeds through the Krebs cycle. When excess acetyl CoA is produced that cannot be processed through the Krebs cycle, the acetyl CoA is converted into triglycerides and fatty acids to be stored in the liver and adipose tissue. **35** If diabetes is uncontrolled, the glucose in the blood is not being taken up and processed by the cells. Although blood glucose levels are high, there is no glucose available to the cells to be converted into energy. Because glucose is lacking, the body turns to other energy sources, including ketones. A side effect of using ketones as fuel is a sweet alcohol smell on the breath. **36** Amino acids are not stored in the body. The individual amino acids are broken down into pyruvate, acetyl CoA, or intermediates of the Krebs cycle, and used for energy or for lipogenesis reactions to be stored as fats. **37** Trypsin and chymotrypsin are released as inactive proenzymes. They are only activated in the small intestine, where they act upon ingested proteins in the food. This helps avoid unintended breakdown of the pancreas or small intestine. **38** Insulin stimulates the uptake of glucose into the cells. In diabetes, the insulin does not function properly; therefore, the blood glucose is unable to be transported across the cell membrane for processing. These patients are unable to process the glucose in their blood and therefore must rely on other sources of fuel. If the disease is not controlled properly, this inability to process the glucose can lead to starvation states even though the patient is eating. **39** When triglycerides and fatty acids are broken down, acetyl CoA is created. If excess acetyl CoA is generated in this process, the excess is used in ketogenesis or the creation of ketones. This creation results from the conversion of acetyl CoA by thiolase into acetoacetyl CoA. This acetoacetyl CoA is subsequently converted into β-hydroxybutyrate, the most common ketone in the body. **40** When blood flows to the outer layers of the skin or to the extremities, heat is lost to the environment by the mechanisms of conduction, convection, or radiation. This will cool the blood and the body. Vasoconstriction helps increase the core body temperature by preventing the flow of blood to the outer layer of the skin and outer parts of the extremities. **41** The ingestion of food stimulates digestion and processing of the carbohydrates, proteins, and fats. This breakdown of food triggers glycolysis, the Krebs cycle, the electron transport chain, fatty acid oxidation, lipogenesis, and amino acid oxidation to produce energy. Heat is a byproduct of those reactions. **42** Factors that influence weight gain are food intake (both quantity and quality), environmental factors, height, exercise level, some drugs or disease states, and genes. **43** Although these foods technically do not have fat added, many times a significant amount of sugar is added to sweeten the food and make it taste better. These foods are non-fat; however, they can lead to significant fat storage or weight gain because the excess sugar is broken down into pyruvate, but overloads the Krebs cycle. When this happens, the sugar is converted into fat through lipogenesis and stored in adipose tissues.

## Chapter 25

**1** B **2** C **3** D **4** C **5** B **6** C **7** D **8** A **9** A **10** B **11** C **12** C **13** B **14** D **15** B **16** B **17** A **18** B **19** B **20** A **21** C **22** D **23** D **24** A **25** D **26** A **27** B **28** B **29** C **30** D **31** The presence of white blood cells found in the urine suggests urinary tract infection. **32** Diabetes mellitus would result in urine containing glucose, and diabetes insipidus would produce urine with very low osmolarity (low specific gravity, dilute). **33** The longer urethra of males means bacteria must travel farther to the bladder to cause an infection. **34** Forceful urination is accomplished by contraction of abdominal muscles. **35** Retroperitoneal anchoring, renal fat pads, and ribs provide protection to the kidney. **36** The renal portal system has an artery between the first and second capillary bed. The others have a vein. **37** The structures found in the renal hilum are arteries, veins, ureters, lymphatics, and nerves. **38** The structures that make up the renal corpuscle are the glomerulus, Bowman's capsule, and PCT. **39** The major structures comprising the filtration membrane are fenestrations and podocyte fenestra, fused basement membrane, and filtration slits. **40** Net filtration pressure (NFP) = glomerular blood hydrostatic pressure (GBHP) – [capsular hydrostatic pressure (CHP) + blood colloid osmotic pressure (BCOP)] **41** Symptoms of kidney failure are weakness, lethargy, shortness of breath, widespread edema, anemia, metabolic acidosis or alkalosis, heart arrhythmias, uremia, loss of appetite, fatigue, excessive urination, and oliguria. **42** The vasa recta and loop of Henle are involved in countercurrent multiplication. **43** The approximate osmolarities are: CT = 300; deepest loop = 1200; DCT = 100; and collecting ducts = 100–1200. **44** Sodium concentration in the filtrate increases when GFR increases; it will decrease when GFR decreases. **45** To excrete more $Na^+$ in the urine, increase the flow rate. **46** The liver produces angiotensinogen, the lungs produce ACE, and the kidneys produce renin. **47** PTH affects absorption and reabsorption of calcium. **48** When first discovered, it was named for its known activity—vasoconstriction. **49** In cases of diabetes mellitus, there is more glucose present than the kidney can recover and the excess glucose is lost in the urine. It possesses osmotic character so that it attracts water to the forming urine. **50** Protein has osmotic properties. If there is not enough protein in the blood, water will be attracted to the interstitial space and the cell cytoplasm resulting in tissue edema. **51** The three electrolytes are most closely regulated by the kidney are calcium, sodium, and potassium.

## Chapter 26

**1** The interstitial fluid (IF). **2** Fluid enters the capillaries from interstitial spaces. **3** Drinking seawater dehydrates the body as the body must pass sodium through the kidneys, and water follows. **4** Because oxygen is reduced, the respiratory rate increases to accommodate, and hyperventilation removes $CO_2$ faster than normal, resulting in alkalosis. **5** A **6** B **7** C **8** C **9** D **10** A **11** B **12** B **13** A **14** A **15** B **16** C **17** B **18** C **19** B **20** A **21** B **22** C **23** D **24** A **25** B **26** B **27** C **28** A **29** C **30** B **31** There are additional negatively charged molecules in plasma besides chloride. The additional sodium balances the total negative charges. **32** Fluid is moved by a combination of osmotic and hydrostatic pressures. The osmotic pressure results from differences in solute concentrations across cell membranes. Hydrostatic pressure results from the pressure of blood as it enters a capillary system, forcing some fluid out of the vessel into the surrounding tissues. **33** ADH constricts the arterioles in the peripheral circulation, limiting blood to the extremities and increasing the blood supply to the core of the body. ADH also causes the epithelial cells lining the renal collecting tubules to move water channel proteins called aquaporins from the sides of the cells to the apical surface. This greatly increases the passage of water from the renal filtrate through the wall of the collecting tubule as well as the reabsorption of water into the bloodstream. **34** Any imbalance of water entering or leaving the body will create an osmotic imbalance that will adversely affect cell and tissue function. **35** Very little of the carbon dioxide in the blood is carried dissolved in the plasma. It is transformed into carbonic acid and then into bicarbonate in order to mix in plasma for transportation to the lungs, where it reverts back to its gaseous form. **36** Without having an absolute excess or deficiency of a substance, one can have too much or too little of that substance in a given compartment. Such a relative increase or decrease is due to a redistribution of water or the ion in the body's compartments. This may be due to the loss of water in the blood, leading to a hemoconcentration or dilution of the ion in tissues due to edema. **37** Bicarbonate ions are freely filtered through the glomerulus. They cannot pass freely into the renal tubular cells and must be converted into $CO_2$ in the filtrate, which can pass through the cell membrane. Sodium ions are reabsorbed at the membrane, and hydrogen ions are expelled into the filtrate. The hydrogen ions combine with bicarbonate, forming carbonic acid, which dissociates into $CO_2$ gas and water. The gas diffuses into the renal cells where carbonic anhydrase catalyzes its conversion back into a bicarbonate ion, which enters the blood. **38** Carbonic acid blood levels are controlled through the respiratory system by the expulsion of $CO_2$ from the lungs. The formula for the production of bicarbonate ions is reversible if the concentration of $CO_2$ decreases. As this happens in the lungs, carbonic acid is converted into a gas, and the concentration of the acid decreases. The rate of respiration determines the amount of $CO_2$ exhaled. If the rate increases, less acid is in the blood; if the rate decreases, the blood can become more acidic. **39** Respiratory acidosis is present as evidenced by the decreased pH and increased $pCO_2$, with some compensation as shown by the increased total $HCO_3^-$. His asthma has compromised his respiratory functions, and excess $CO_2$ is being retained in his blood. **40** Metabolic alkalosis is present as evidenced by the increased pH and increased $HCO_3^-$, without compensation as seen in the normal $pCO_2$. The bulimia has caused excessive loss of hydrochloric acid from the stomach and a loss of hydrogen ions from the body, resulting in an excess of bicarbonate ions in the blood.

## Chapter 27

**1** Sperm remain in the epididymis until they degenerate. **2** Sperm enter the prostate. **3** The fimbriae sweep the oocyte into the uterine tube. **4** The oocyte may not enter the tube and may enter the pelvic cavity. **5** The testes are located in the abdomen. **6** b **7** a **8** b **9** a **10** c **11** d **12** a **13** b **14** c **15** b **16** d **17** c **18** b **19** d **20** A single gamete must combine with a gamete from an individual of the opposite sex to produce a fertilized egg, which has a complete set of chromosomes and is the first cell of a new

individual. **21** Unlike somatic cells, sperm are haploid. They also have very little cytoplasm. They have a head with a compact nucleus covered by an acrosome filled with enzymes, and a mid-piece filled with mitochondria that power their movement. They are motile because of their tail, a structure containing a flagellum, which is specialized for movement. **22** The three accessory glands make the following contributions to semen: the seminal vesicle contributes about 60 percent of the semen volume, with fluid that contains large amounts of fructose to power the movement of sperm; the prostate gland contributes substances critical to sperm maturation; and the bulbourethral glands contribute a thick fluid that lubricates the ends of the urethra and the vagina and helps to clean urine residues from the urethra. **23** During sexual arousal, nitric oxide (NO) is released from nerve endings near blood vessels within the corpora cavernosa and corpus spongiosum. The release of NO activates a signaling pathway that results in relaxation of the smooth muscles that surround the penile arteries, causing them to dilate. This dilation increases the amount of blood that can enter the penis, and induces the endothelial cells in the penile arterial walls to secrete NO, perpetuating the vasodilation. The rapid increase in blood volume fills the erectile chambers, and the increased pressure of the filled chambers compresses the thin-walled penile venules, preventing venous drainage of the penis. An erection is the result of this increased blood flow to the penis and reduced blood return from the penis. **24** Testosterone production by the body would be reduced if a male were taking anabolic steroids. This is because the hypothalamus responds to rising testosterone levels by reducing its secretion of GnRH, which would in turn reduce the anterior pituitary's release of LH, finally reducing the manufacture of testosterone in the testes. **25** The sperm must swim upward in the vagina, through the cervix, and then through the body of the uterus to one or the other of the two uterine tubes. Fertilization generally occurs in the uterine tube. **26** Meiosis in the man results in four viable haploid sperm, whereas meiosis in the woman results in a secondary oocyte and, upon completion following fertilization by a sperm, one viable haploid ovum with abundant cytoplasm and up to three polar bodies with little cytoplasm that are destined to die. **27** As a result of the degradation of the corpus luteum, a decline in progesterone concentrations triggers the shedding of the endometrial lining, marking the menses phase of the menstrual cycle. Low progesterone levels also reduce the negative feedback that had been occurring at the hypothalamus and pituitary, and result in the release of GnRH and, subsequently, FSH and LH. FSH stimulates tertiary follicles to grow and granulosa and theca cells begin to produce increased amounts of estrogen. High estrogen concentrations stimulate the endometrial lining to rebuild, marking the proliferative phase of the menstrual cycle. The high estrogen concentrations will eventually lead to a decrease in FSH because of negative feedback, resulting in atresia of all but one of the developing tertiary follicles. The switch to positive feedback that occurs with elevated estrogen production from the dominant follicle stimulates the LH surge that will trigger ovulation. The luteinization of the granulosa cells of the collapsed follicle forms the progesterone-producing corpus luteum. Progesterone from the corpus luteum causes the endometrium to prepare for implantation, in part by secreting nutrient-rich fluid. This marks the secretory phase of the menstrual cycle. Finally, in a non-fertile cycle, the corpus luteum will degrade and menses will occur. **28** Endometrial tissue proliferating outside of the endometrium—for example, in the uterine tubes, on the ovaries, or within the pelvic cavity—could block the passage of sperm, ovulated oocytes, or a zygote, thus reducing fertility. **29** As an individual approaches puberty, two changes in sensitivity occur. The first is a decrease of sensitivity in the hypothalamus and pituitary to negative feedback, meaning that it takes increasingly larger concentrations of sex steroid hormones to stop the production of LH and FSH. The second change in sensitivity is an increase in the sensitivity of the gonads to the FSH and LH signals, meaning that the gonads of adults are more responsive to gonadotropins than are the gonads of children. As a result of these two changes, the levels of LH and FSH slowly increase and lead to the enlargement and maturation of the gonads, which in turn leads to secretion of higher levels of sex hormones and the initiation of spermatogenesis and folliculogenesis. **30** The internal reproductive structures form from one of two rudimentary duct systems in the embryo. Testosterone secretion stimulates growth of the male tract, the Wolffian duct. Secretions of sustentacular cells trigger a degradation of the female tract, the Müllerian duct. Without these stimuli, the Müllerian duct will develop and the Wolffian duct will degrade, resulting in a female embryo. **31** If the *SRY* gene were not functional, the XY individual would be genetically a male, but would develop female reproductive structures.

## Chapter 28

**1** The first structure shown is the morula. The blastocoel appears at approximately 20 seconds. The movie ends with the hatching of the conceptus. **2** Neurulation starts in week 4. **3** A regular heartbeat can be detected at approximately 8 weeks. **4** C **5** A **6** B **7** C **8** A **9** D **10** B **11** A **12** B **13** C **14** A **15** C **16** B **17** C **18** A **19** C **20** B **21** D **22** B **23** A **24** B **25** C **26** B **27** A **28** D **29** C **30** C **31** D **32** The process of capacitation appears to be incomplete. Capacitation increases sperm motility and makes the sperm membrane more fragile. This enables it to release its digestive enzymes during the acrosomal reaction. When capacitation is inadequate, sperm cannot reach the oocyte membrane. **33** Sherrise's concern is valid. Sperm may be viable for up to 4 days; therefore, it is entirely possible that capacitated sperm are still residing in her uterine tubes and could fertilize the oocyte she has just ovulated. **34** The timing of this discomfort and bleeding suggests that it is probably caused by implantation of the blastocyst into the uterine wall. **35** Folate, one of the B vitamins, is important for the healthy formation of the embryonic neural tube, which occurs in the first few weeks following conception—often before a woman even realizes she is pregnant. A folate-deficient environment increases the risk of a neural tube defect, such as spina bidifa, in the newborn. **36** Circulatory shunts bypass the fetal lungs and liver, bestowing them with just enough oxygenated blood to fulfill their metabolic requirements. Because these organs are only semifunctional in the fetus, it is more efficient to bypass them and divert oxygen and nutrients to the organs that need it more. **37** Premature lungs may not have adequate surfactant, a molecule that reduces surface tension in the lungs and assists proper lung expansion after birth. If the lungs do not expand properly, the newborn will develop hypoxia and require supplemental oxygen or other respiratory support. **38** Devin is very likely experiencing Braxton Hicks contractions, also known as false labor. These are mild contractions that do not promote cervical dilation and are not associated with impending birth. They will probably dissipate with rest. **39** Janine is 41 weeks pregnant, and the mild contractions she has been experiencing "for days" have dilated her cervix to 2 cm. These facts suggest that she is in labor, but that the labor is not progressing appropriately. Pitocin is a pharmaceutical preparation of synthetic prostaglandins and oxytocin, which will increase the frequency and strength of her contractions and help her labor to progress to birth. **40** The first breath inflates the lungs, which drops blood pressure

throughout the pulmonary system, as well as in the right atrium and ventricle. In response to this pressure change, the flow of blood temporarily reverses direction through the foramen ovale, moving from the left to the right atrium, and blocking the shunt with two flaps of tissue. The increased oxygen concentration also constricts the ductus arteriosus, ensuring that these shunts no longer prevent blood from reaching the lungs to be oxygenated. **41** The newborn's kidneys are immature and inefficient at concentrating urine. Therefore, newborns produce very dilute urine—in a sense, wasting fluid. This increases their risk for dehydration, and makes it critical that caregivers provide newborns with enough fluid, especially during bouts of vomiting or diarrhea. **42** Milk is secreted by lactocytes into alveoli. Suckling stimulates the contraction of myoepithelial cells that squeeze milk into lactiferous ducts. It then collects in lactiferous sinuses and is secreted through the nipple pores. **43** It takes time to establish a balance between milk supply and milk demand. When breastfeeding stops abruptly, it takes time for the supply to fall. Excessive milk supply creates breast engorgement and leakage. **44** By using large sample sizes, Mendel minimized the effect of random variability resulting from chance. This allowed him to identify true ratios corresponding to dominant–recessive inheritance. **45** The only way an affected daughter could be born is if the female carrier mated with a male who was affected. In this case, 50 percent of the daughters would be affected. Alternatively, but exceedingly unlikely, the daughter could become affected by a spontaneous mutation.

# REFERENCES


## 3.2 The Cytoplasm and Cellular Organelles

Kolata, G. Severe diet doesn't prolong life, at least in monkeys. *New York Times* [Internet]. 2012 Aug. 29 [cited 2013 Jan 21]; Available from:

http://www.nytimes.com/2012/08/30/science/low-calorie-diet-doesnt-prolong-life-study-of-monkeys-finds.html?_r=2&ref=caloricrestriction& (http://www.nytimes.com/2012/08/30/science/low-calorie-diet-doesnt-prolong-life-study-of-monkeys-finds.html?_r=2&ref=caloricrestriction&)

## 4.5 Nervous Tissue Mediates Perception and Response

Stern, P. Focus issue: getting excited about glia. Science [Internet]. 2010 [cited 2012 Dec 4]; 3(147):330-773. Available from:

http://stke.sciencemag.org/cgi/content/abstract/sigtrans;3/147/eg11 (http://stke.sciencemag.org/cgi/content/abstract/sigtrans;3/147/eg11)

Ming GL, Song H. Adult neurogenesis in the mammalian central nervous system. Annu. Rev. Neurosci. 2005 [cited 2012 Dec 4]; 28:223–250.

## 4.6 Tissue Injury and Aging

Emerson, RW. Old age. Atlantic. 1862 [cited 2012 Dec 4]; 9(51):134–140.

## 5.3 Functions of the Integumentary System

American Academy of Dermatology (US). Tattoos and body piercings [Internet]. Schaumburg, IL; c2013 [cited 2012 Nov 1]. Available from: http://www.aad.org/media-resources/stats-and-facts/prevention-and-care/tattoos-and-body-piercings/ (http://www.aad.org/media-resources/stats-and-facts/prevention-and-care/tattoos-and-body-piercings/) .

## 5.4 Diseases, Disorders, and Injuries of the Integumentary System

American Cancer Society (US). Skin cancer: basal and squamous cell [Internet]. c2013 [cited 2012 Nov 1]. Available from: http://www.cancer.org/acs/groups/cid/documents/webcontent/003139-pdf.pdf (http://www.cancer.org/acs/groups/cid/documents/webcontent/003139-pdf.pdf) .

Lucile Packard Children's Hospital at Stanford (US). Classification and treatment of burns [Internet]. Palo Alto (CA). c2012 [cited 2012 Nov 1]. Available from: http://www.lpch.org/diseasehealthinfo/healthlibrary/burns/classify.html (http://www.lpch.org/diseasehealthinfo/healthlibrary/burns/classify.html) .

Mayo Clinic (US). Basal cell carcinoma [Internet]. Scottsdale (AZ); c2012 [cited 2012 Nov 1]. Available from: http://www.mayoclinic.com/health/basal-cell-carcinoma/ds00925/dsection=treatments-and-drugs (http://www.mayoclinic.com/health/basal-cell-carcinoma/ds00925/dsection=treatments-and-drugs) .

Beck, J. FYI: how much can a human body sweat before it runs out? Popular Science [Internet]. New York (NY); c2012 [cited 2012 Nov 1]. Available from:http://www.popsci.com/science/article/2011-01/fyi-how-much-can-human-body-sweat-it-runs-out (http://www.popsci.com/science/article/2011-01/fyi-how-much-can-human-body-sweat-it-runs-out) .

Skin Cancer Foundation (US). Skin cancer facts [Internet]. New York (NY); c2013 [cited 2012 Nov 1]. Available from: http://www.skincancer.org/skin-cancer-information/skin-cancer-facts#top (http://www.skincancer.org/skin-cancer-information/skin-cancer-facts#top) .

## 7.2 The Skull

Centers for Disease Control and Prevention (US). Injury prevention and control: traumatic brain injury [Internet]. Atlanta, GA; [cited 2013 Mar 18]. Available from: http://www.cdc.gov/traumaticbraininjury/statistics.html (http://www.cdc.gov/traumaticbraininjury/statistics.html) .

## 12.1 Basic Structure and Function of the Nervous System

Kramer, PD. Listening to prozac. 1st ed. New York (NY): Penguin Books; 1993.

## 18.6 Blood Typing

American Red Cross (US). Blood types [Internet]. c2013 [cited 2013 Apr 3]. Available from: http://www.redcrossblood.org/learn-about-blood/blood-types (http://www.redcrossblood.org/learn-about-blood/blood-types) 2013

## 20.4 Homeostatic Regulation of the Vascular System

Centers for Disease Control and Prevention (US). Getting blood pressure under control: high blood pressure is out of control for too many Americans [Internet]. Atlanta (GA); [cited 2013 Apr 26]. Available from: http://www.cdc.gov/features/vitalsigns/hypertension/ (http://www.cdc.gov/features/vitalsigns/hypertension/)

## 21.7 Transplantation and Cancer Immunology

Robinson J, Mistry K, McWilliam H, Lopez R, Parham P, Marsh SG. Nucleic acid research. IMGT/HLA Database [Internet]. 2011 [cited 2013 Apr 1]; 39:D1171–1176. Available from: http://europepmc.org/abstract/MED/21071412 (http://europepmc.org/abstract/MED/21071412)

Robinson J, Malik A, Parham P, Bodmer JG, Marsh SG. Tissue antigens. IMGT/HLA Database [Internet]. 2000 [cited 2013 Apr 1]; 55(3):280–287. Available from: http://europepmc.org/abstract/MED/10777106/reload=0;jsessionid=otkdw3M0TIVSa2zhvimg.6 (http://europepmc.org/abstract/MED/10777106/reload=0;jsessionid=otkdw3M0TIVSa2zhvimg.6)

## 22.1 Organs and Structures of the Respiratory System

Bizzintino J, Lee WM, Laing IA, Vang F, Pappas T, Zhang G, Martin AC, Khoo SK, Cox DW, Geelhoed GC, et al. Association between human rhinovirus C and severity of acute asthma in children. Eur Respir J [Internet]. 2010 [cited 2013 Mar 22]; 37(5):1037–1042. Available from: http://erj.ersjournals.com/gca?submit=Go&gca=erj%3B37%2F5%2F1037&allch= (http://erj.ersjournals.com/gca?submit=Go&gca=erj%3B37%2F5%2F1037&allch=)

Kumar V, Ramzi S, Robbins SL. Robbins Basic Pathology. 7th ed. Philadelphia (PA): Elsevier Ltd; 2005.

Martin RJ, Kraft M, Chu HW, Berns, EA, Cassell GH. A link between chronic asthma and chronic infection. J Allergy Clin Immunol [Internet]. 2001 [cited 2013 Mar 22]; 107(4):595-601. Available from: http://erj.ersjournals.com/gca?submit=Go&gca=erj%3B37%2F5%2F1037&allch= (http://www.jacionline.org/article/S0091-6749(01)31561-0/fulltext)

## 23.3 The Mouth, Pharynx, and Esophagus

van Loon FPL, Holmes SJ, Sirotkin B, Williams W, Cochi S, Hadler S, Lindegren ML. Morbidity and Mortality Weekly Report: Mumps surveillance -- United States, 1988–1993 [Internet]. Atlanta, GA: Center for Disease Control; [cited 2013 Apr 3]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/00038546.htm (http://www.cdc.gov/mmwr/preview/mmwrhtml/00038546.htm) .

## 23.5 The Small and Large Intestines

American Cancer Society (US). Cancer facts and figures: colorectal cancer: 2011–2013 [Internet]. c2013 [cited 2013 Apr 3]. Available from: http://www.cancer.org/Research/CancerFactsFigures/ColorectalCancerFactsFigures/colorectal-cancer-facts-figures-2011-2013-page (http://www.cancer.org/Research/CancerFactsFigures/ColorectalCancerFactsFigures/colorectal-cancer-facts-figures-2011-2013-page) .

The Nutrition Source. Fiber and colon cancer: following the scientific trail [Internet]. Boston (MA): Harvard School of Public Health; c2012 [cited 2013 Apr 3]. Available from: http://www.hsph.harvard.edu/nutritionsource/nutrition-news/fiber-and-colon-cancer/index.html (http://www.hsph.harvard.edu/nutritionsource/nutrition-news/fiber-and-colon-cancer/index.html) .

Centers for Disease Control and Prevention (US). Morbidity and mortality weekly report: notifiable diseases and mortality tables [Internet]. Atlanta (GA); [cited 2013 Apr 3]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101md.htm?s_cid=mm6101md_w (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101md.htm?s_cid=mm6101md_w) .

## 25.10 The Urinary System and Homeostasis

Bagul A, Frost JH, Drage M. Stem cells and their role in renal ischaemia reperfusion injury. Am J Nephrol [Internet]. 2013 [cited 2013 Apr 15]; 37(1):16–29. Available from: http://www.karger.com/Article/FullText/345731 (http://www.karger.com/Article/FullText/345731)

# INDEX

## Symbols



## A

## B



## C

## D

## E

## F

## G

## H

## I

## J



## K



## L

## M

## N



## O

## P

## Q



## R

## S

## T

## U

## V



## W



## X



## Y



## Z

## OpenStax College

OpenStax College is a non-profit organization committed to improving student access to quality learning materials. Our free textbooks are developed and peer-reviewed by educators to ensure they are readable, accurate, and meet the scope and sequence requirements of modern college courses. Through our partnerships with companies and foundations committed to reducing costs for students, OpenStax College is working to improve access to higher education for all.

## Connexions

The technology platform supporting OpenStax College is Connexions (http://cnx.org), one of the world's first and largest open-education projects. Connexions provides students with free online and low-cost print editions of the OpenStax College library and provides instructors with tools to customize the content so that they can have the perfect book for their course.

## Rice University

OpenStax College and Connexions are initiatives of Rice University. As a leading research university with a distinctive commitment to undergraduate education, Rice University aspires to path-breaking research, unsurpassed teaching, and contributions to the betterment of our world. It seeks to fulfill this mission by cultivating a diverse community of learning and discovery that produces leaders across the spectrum of human endeavor.


## Foundation Support

OpenStax College is grateful for the tremendous support of our sponsors. Without their strong engagement, the goal of free access to high-quality textbooks would remain just a dream.


The William and Flora Hewlett Foundation has been making grants since 1967 to help solve social and environmental problems at home and around the world. The Foundation concentrates its resources on activities in education, the environment, global development and population, performing arts, and philanthropy, and makes grants to support disadvantaged communities in the San Francisco Bay Area.


Guided by the belief that every life has equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. In developing countries, it focuses on improving people's health with vaccines and other life-saving tools and giving them the chance to lift themselves out of hunger and extreme poverty. In the United States, it seeks to significantly improve education so that all young people have the opportunity to reach their full potential. Based in Seattle, Washington, the foundation is led by CEO Jeff Raikes and Co-chair William H. Gates Sr., under the direction of Bill and Melinda Gates and Warren Buffett.


Our mission at the Twenty Million Minds Foundation is to grow access and success by eliminating unnecessary hurdles to affordability. We support the creation, sharing, and proliferation of more effective, more affordable educational content by leveraging disruptive technologies, open educational resources, and new models for collaboration between for-profit, nonprofit, and public entities.


The Maxfield Foundation supports projects with potential for high impact in science, education, sustainability, and other areas of social importance.

# Table of Contents (all volumes)

# PREFACE

Welcome to *Human Anatomy and Physiology*, an OpenStax College resource. We created this textbook with several goals in mind: accessibility, customization, and student engagement—helping students reach high levels of academic scholarship. Instructors and students alike will find that this textbook offers a thorough introduction to the content in an accessible format.

## About OpenStax College

OpenStax College is a nonprofit organization committed to improving student access to quality learning materials. Our free textbooks are developed and peer-reviewed by educators to ensure that they are readable, accurate, and organized in accordance with the scope and sequence requirements of today's college courses. Unlike traditional textbooks, OpenStax College resources live online and are owned by the community of educators using them. Through partnerships with companies and foundations committed to reducing costs for students, we are working to improve access to higher education for all. OpenStax College is an initiative of Rice University and is made possible through the generous support of several philanthropic foundations.

## About OpenStax College's Resources

OpenStax College resources provide quality academic instruction. Three key features set our materials apart from others: 1) They can be easily customized by instructors for each class, 2) they are "living" resources that grow online through contributions from science educators, and 3) they are available for free or for a minimal cost.

### Customization

OpenStax College learning resources are conceived and written with flexibility in mind so that they can be customized for each course. Our textbooks provide a solid foundation on which instructors can build their own texts. Instructors can select the sections that are most relevant to their curricula and create a textbook that speaks directly to the needs of their students. Instructors are encouraged to expand on existing examples in the text by adding unique context via geographically localized applications and topical connections.

*Human Anatomy and Physiology* can be easily customized using our online platform (https://openstaxcollege.org/textbooks/anatomy-and-physiology/adapt). The text is arranged in a modular chapter format. Simply select the content most relevant to your syllabus and create a textbook that addresses the needs of your class. This customization feature will ensure that your textbook reflects the goals of your course.

### Curation

To broaden access and encourage community curation, *Human Anatomy and Physiology* is "open source" under a Creative Commons Attribution (CC BY) license. Members of the scientific community are invited to submit examples, emerging research, and other feedback to enhance and strengthen the material, keeping it current and relevant for today's students. Submit your suggestions to info@openstaxcollege.org, and check in on edition status, alternate versions, errata, and news on the StaxDash at http://openstaxcollege.org.

### Cost

Our textbooks are available for free online, and in low-cost print and tablet editions.

## About *Human Anatomy and Physiology*

*Human Anatomy and Physiology* is designed for the two-semester anatomy and physiology course taken by life science and allied health students. It supports effective teaching and learning, and prepares students for further learning and future careers. The text focuses on the most important concepts and aims to minimize distracting students with more minor details.

The development choices for this textbook were made with the guidance of hundreds of faculty who are deeply involved in teaching this course. These choices led to innovations in art, terminology, career orientation, practical applications, and multimedia-based learning, all with a goal of increasing relevance to students. We strove to make the discipline meaningful and memorable to students, so that they can draw from it a working knowledge that will enrich their future studies.

### Coverage and Scope

The units of our *Human Anatomy and Physiology* textbook adhere to the scope and sequence followed by most two-semester courses nationwide.

### Unit 1: Levels of Organization

Chapters 1–4 provide students with a basic understanding of human anatomy and physiology, including its language, the levels of organization, and the basics of chemistry and cell biology. These chapters provide a foundation for the further study

of the body. They also focus particularly on how the body's regions, important chemicals, and cells maintain homeostasis.
Chapter 1 An Introduction to the Human Body
Chapter 2 The Chemical Level of Organization
Chapter 3 The Cellular Level of Organization
Chapter 4 The Tissue Level of Organization

### Unit 2: Support and Movement

In Chapters 5–11, students explore the skin, the largest organ of the body, and examine the body's skeletal and muscular systems, following a traditional sequence of topics. This unit is the first to walk students through specific systems of the body, and as it does so, it maintains a focus on homeostasis as well as those diseases and conditions that can disrupt it.
Chapter 5 The Integumentary System
Chapter 6 Bone and Skeletal Tissue
Chapter 7 The Axial Skeleton
Chapter 8 The Appendicular Skeleton
Chapter 9 Joints
Chapter 10 Muscle Tissue
Chapter 11 The Muscular System

### Unit 3: Regulation, Integration, and Control

Chapters 12–17 help students answer questions about nervous and endocrine system control and regulation. In a break with the traditional sequence of topics, the special senses are integrated into the chapter on the somatic nervous system. The chapter on the neurological examination offers students a unique approach to understanding nervous system function using five simple but powerful diagnostic tests.
Chapter 12 Introduction to the Nervous System
Chapter 13 The Anatomy of the Nervous System
Chapter 14 The Somatic Nervous System
Chapter 15 The Autonomic Nervous System
Chapter 16 The Neurological Exam
Chapter 17 The Endocrine System

### Unit 5: Energy, Maintenance, and Environmental Exchange

In Chapters 22–26, students discover the interaction between body systems and the outside environment for the exchange of materials, the capture of energy, the release of waste, and the overall maintenance of the internal systems that regulate the exchange. The explanations and illustrations are particularly focused on how structure relates to function.
Chapter 22 The Respiratory System
Chapter 23 The Digestive System
Chapter 24 Nutrition and Metabolism
Chapter 25 The Urinary System
Chapter 26 Fluid, Electrolyte, and Acid–Base Balance

### Unit 6: Human Development and the Continuity of Life

The closing chapters examine the male and female reproductive systems, describe the process of human development and the different stages of pregnancy, and end with a review of the mechanisms of inheritance.
Chapter 27 The Reproductive System
Chapter 28 Development and Genetic Inheritance

### Pedagogical Foundation and Features

*Human Anatomy and Physiology* is designed to promote scientific literacy. Throughout the text, you will find features that engage the students by taking selected topics a step further.

**Homeostatic Imbalances** discusses the effects and results of imbalances in the body.

**Disorders** showcases a disorder that is relevant to the body system at hand. This feature may focus on a specific disorder, or a set of related disorders.

**Diseases** showcases a disease that is relevant to the body system at hand.

**Aging** explores the effect aging has on a body's system and specific disorders that manifest over time.

**Career Connections** presents information on the various careers often pursued by allied health students, such as medical technician, medical examiner, and neurophysiologist. Students are introduced to the educational requirements for and day-to-day responsibilities in these careers.

**Everyday Connections** tie anatomical and physiological concepts to emerging issues and discuss these in terms of everyday life. Topics include "Anabolic Steroids" and "The Effect of Second-Hand Tobacco Smoke."

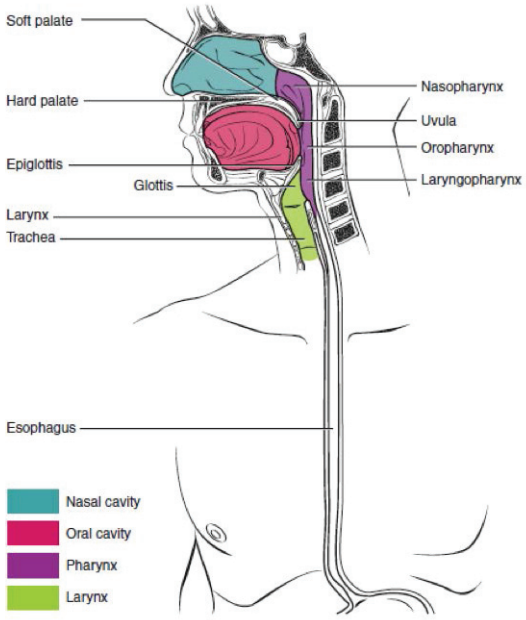
**Interactive Links** direct students to online exercises, simulations, animations, and videos to add a fuller context to core content and help improve understanding of the material. Many features include links to the University of Michigan's interactive WebScopes, which allow students to zoom in on micrographs in the collection. These resources were vetted by reviewers and other subject matter experts to ensure that they are effective and accurate. We strongly

urge students to explore these links, whether viewing a video or inputting data into a simulation, to gain the fullest experience and to learn how to search for information independently.

## Dynamic, Learner-Centered Art

Our unique approach to visuals is designed to emphasize only the components most important in any given illustration. The art style is particularly aimed at focusing student learning through a powerful blend of traditional depictions and instructional innovations.

Much of the art in this book consists of black line illustrations. The strongest line is used to highlight the most important structures, and shading is used to show dimension and shape. Color is used sparingly to highlight and clarify the primary anatomical or functional point of the illustration. This technique is intended to draw students' attention to the critical learning point in the illustration, without distraction from excessive gradients, shadows, and highlights. Full color is used when the structure or process requires it (for example, muscle diagrams and cardiovascular system illustrations).

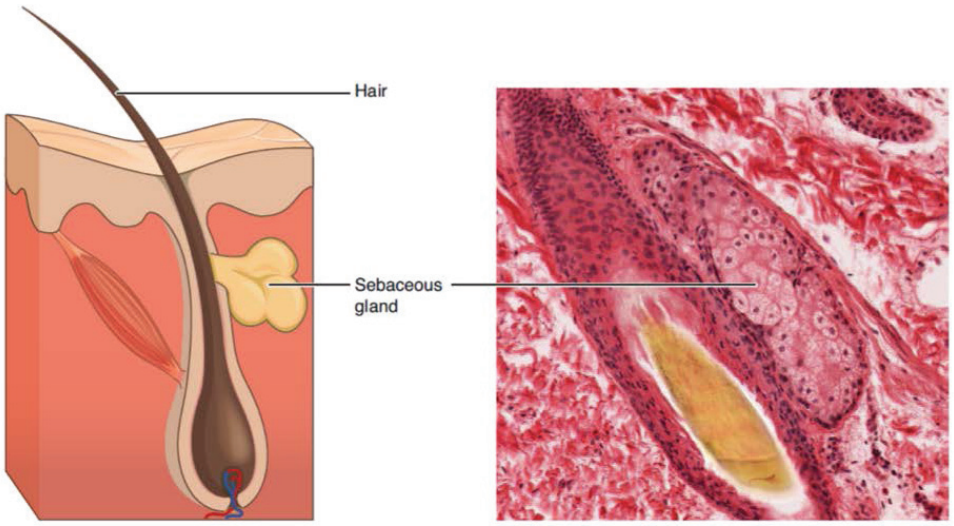



By highlighting the most important portions of the illustration, the artwork helps students focus on the most important points, without overwhelming them.

## Micrographs

Micrograph magnifications have been calculated based on the objective provided with the image. If a micrograph was recorded at 40×, and the image was magnified an additional 2×, we calculated the final magnification of the micrograph to be 80×.

Please note that, when viewing the textbook electronically, the micrograph magnification provided in the text does not take into account the size and magnification of the screen on your electronic device. There may be some variation.




These glands secrete oils that lubricate and protect the skin. LM × 400. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

### Learning Resources

The following resources are (or will be) available in addition to main text:

PowerPoint slides: For each chapter, the illustrations are presented, one per slide, with their respective captions.

Pronunciation guide: A subset of the text's key terms are presented with easy-to-follow phonetic transcriptions. For example, blastocyst is rendered as "blas'to-sist"

## About Our Team

### Senior Contributors

| | |
|---|---|
| J. Gordon Betts | Tyler Junior College |
| Peter Desaix | University of North Carolina at Chapel Hill |
| Eddie Johnson | Central Oregon Community College |
| Jody E. Johnson | Arapahoe Community College |
| Oksana Korol | Aims Community College |
| Dean Kruse | Portland Community College |
| Brandon Poe | Springfield Technical Community College |
| James A. Wise | Hampton University |
| Mark Womble | Youngstown State University |
| Kelly A. Young | California State University, Long Beach |

### Advisor

Robin J. Heyden

### Other Contributors

| | |
|---|---|
| Kim Aaronson | Aquarius Institute; Triton College |
| Lopamudra Agarwal | Augusta Technical College |
| Gary Allen | Dalhousie University |
| Robert Allison | McLennan Community College |
| Heather Armbruster | Southern Union State Community College |
| Timothy Ballard | University of North Carolina Wilmington |

| | |
|---|---|
| Matthew Barlow | Eastern New Mexico University |
| William Blaker | Furman University |
| Julie Bowers | East Tennessee State University |
| Emily Bradshaw | Florida Southern College |
| Nishi Bryska | University of North Carolina, Charlotte |
| Susan Caley Opsal | Illinois Valley Community College |
| Boyd Campbell | Southwest College of Naturopathic Medicine and Health Sciences |
| Ann Caplea | Walsh University |
| Marnie Chapman | University of Alaska, Sitka |
| Barbara Christie-Pope | Cornell College |
| Kenneth Crane | Texarkana College |
| Maurice Culver | Florida State College at Jacksonville |
| Heather Cushman | Tacoma Community College |
| Noelle Cutter | Molloy College |
| Lynnette Danzl-Tauer | Rock Valley College |
| Jane Davis | Aurora University |
| AnnMarie DelliPizzi | Dominican College |
| Susan Dentel | Washtenaw Community College |
| Pamela Dobbins | Shelton State Community College |
| Patty Dolan | Pacific Lutheran University |
| Sondra Dubowsky | McLennan Community College |
| Peter Dukehart | Three Rivers Community College |
| Ellen DuPré | Central College |
| Elizabeth DuPriest | Warner Pacific College |
| Pam Elf | University of Minnesota |
| Sharon Ellerton | Queensborough Community College |
| Carla Endres | Utah State University - College of Eastern Utah: San Juan Campus |
| Myriam Feldman | Lake Washington Institute of Technology; Cascadia Community College |
| Greg Fitch | Avila University |
| Lynn Gargan | Tarant County College |
| Michael Giangrande | Oakland Community College |
| Chaya Gopalan | St. Louis College of Pharmacy |
| Victor Greco | Chattahoochee Technical College |
| Susanna Heinze | Skagit Valley College |
| Ann Henninger | Wartburg College |
| Dale Horeth | Tidewater Community College |
| Michael Hortsch | University of Michigan |
| Rosemary Hubbard | Marymount University |
| Mark Hubley | Prince George's Community College |
| Branko Jablanovic | College of Lake County |
| Norman Johnson | University of Massachusetts Amherst |
| Mark Jonasson | North Arkansas College |
| Jeff Keyte | College of Saint Mary |
| William Kleinelp | Middlesex County College |

| | |
|---|---|
| Leigh Kleinert | Grand Rapids Community College |
| Brenda Leady | University of Toledo |
| John Lepri | University of North Carolina, Greensboro |
| Sarah Leupen | University of Maryland, Baltimore County |
| Lihua Liang | Johns Hopkins University |
| Robert Mallet | University of North Texas Health Science Center |
| Bruce Maring | Daytona State College |
| Elisabeth Martin | College of Lake County |
| Natalie Maxwell | Carl Albert State College, Sallisaw |
| Julie May | William Carey University |
| Debra McLaughlin | University of Maryland University College |
| Nicholas Mitchell | St. Bonaventure University |
| Phillip Nicotera | St. Petersburg College |
| Mary Jane Niles | University of San Francisco |
| Ikemefuna Nwosu | Parkland College; Lake Land College |
| Betsy Ott | Tyler Junior College |
| Ivan Paul | John Wood Community College |
| Aaron Payette | College of Southern Nevada |
| Scott Payne | Kentucky Wesleyan College |
| Cameron Perkins | South Georgia College |
| David Pfeiffer | University of Alaska, Anchorage |
| Thomas Pilat | Illinois Central College |
| Eileen Preston | Tarrant County College |
| Mike Pyle | Olivet Nazarene University |
| Robert Rawding | Gannon University |
| Jason Schreer | State University of New York at Potsdam |
| Laird Sheldahl | Mt. Hood Community College |
| Brian Shmaefsky | Lone Star College System |
| Douglas Sizemore | Bevill State Community College |
| Susan Spencer | Mount Hood Community College |
| Cynthia Standley | University of Arizona |
| Robert Sullivan | Marist College |
| Eric Sun | Middle Georgia State College |
| Tom Swenson | Ithaca College |
| Kathleen Tallman | Azusa Pacific University |
| Rohinton Tarapore | University of Pennsylvania |
| Elizabeth Tattersall | Western Nevada College |
| Mark Thomas | University of Northern Colorado |
| Janis Thompson | Lorain County Community College |
| Rita Thrasher | Pensacola State College |
| David Van Wylen | St. Olaf College |
| Lynn Wandrey | Mott Community College |
| Margaret Weck | St. Louis College of Pharmacy |
| Kathleen Weiss | George Fox University |

| | |
|---|---|
| Neil Westergaard | Williston State College |
| David Wortham | West Georgia Technical College |
| Umesh Yadav | University of Texas Medical Branch |
| Tony Yates | Oklahoma Baptist University |
| Justin York | Glendale Community College |
| Cheri Zao | North Idaho College |
| Elena Zoubina | Bridgewater State University; Massasoit Community College |

## Special Thanks

OpenStax College wishes to thank the Regents of University of Michigan Medical School for the use of their extensive micrograph collection. Many of the UM micrographs that appear in *Human Anatomy and Physiology* are interactive WebScopes, which students can explore by zooming in and out.

We also wish to thank the Open Learning Initiative at Carnegie Mellon University, with whom we shared and exchanged resources during the development of *Human Anatomy and Physiology*.

# INDEX

## Symbols



## A

## B



## C

## D

## E

## F

## G

## H

## I

## J



## K



## L

## M

## N



## O

## P

## Q



## R

## S

## T

## U

## V



## W



## X



## Y



## Z