PHYSIOLOGY

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Reference: Human Physiology 15th ed. By Stuart Fox

VANDER' S Human Physiology 15th ed. By ERIC P. WIDMAIER

Anatomy and Physiology, 2nd ed , By Robin J. Heyden

1.1. INTRODUCTION TO PHYSIOLOGY

Human physiology is the study of how the human body functions, with emphasis on specific cause-and-effect mechanisms. Knowledge of these mechanisms has been obtained experimentally through applications of the scientific method.

LEARNING OUTCOMES

After studying this section, you should be able to:

Describe the scientific study of human physiology.

Describe the characteristics of the scientific method.

Physiology (from the Greek physis = nature; logos = study) is the study of biological function—of how the body works, from molecular mechanisms within cells to the actions of tissues, organs, and systems, and how the organism as a whole accomplishes particular tasks essential for life. In the study of physiology, the emphasis is on mechanisms—with questions that begin with the word how and answers that involve cause-and-effect sequences. These sequences can be woven into larger and larger stories that include descriptions of the structures involved (anatomy) and that overlap with the sciences of chemistry and physics.

The separate facts and relationships of these cause-and-effect sequences are derived empirically from experimental evidence. Explanations that seem logical are not necessarily true; they are only as valid as the data on which they are based, and they can change as new techniques are developed and further experiments are performed. The ultimate objective of physiological research is to understand the normal functioning of cells, organs, and systems. A related science—**pathophysiology**—is concerned with how physiological processes are altered in disease or injury.

Pathophysiology and the study of normal physiology complement one another. For example, a standard technique for investigating the functioning of an organ is to observe what happens when the organ is surgically removed from an experimental animal or when its function is altered in a specific way. This study is often aided by "experiments of nature"—diseases—that involve specific damage to the functioning of an organ. The study of disease processes has thus aided our understanding of normal functioning, and the study of normal physiology has provided much of the scientific basis of modern medicine. This relationship is recognized by the Nobel Prize committee, whose members award prizes in the category "Physiology or Medicine."

The physiology of invertebrates and of different vertebrate groups is studied in the science of **comparative physiology**. Much of the knowledge gained from comparative physiology has benefited the study of human physiology. This is because animals, including humans, are more alike than they are different. This is especially true when comparing humans with other mammals. The small differences in physiology between humans and other mammals can be of crucial importance in the development of pharmaceutical drugs (discussed later in this section), but these differences are relatively slight in the overall study of physiology.

History of Physiology

The Greek philosopher Aristotle (384–322 B.C.) speculated on the function of the human body, but another ancient Greek, Erasistratus (304–250? B.C.), is considered to be the first to study physiology because he attempted to applyphysical laws to understand human function. Galen (A.D. 130–201) wrote widely on the subject and was considered the supreme authority until the Renaissance.

TABLE 1.1 | History of Twentieth- and Twenty-First-Century Physiology (two citations per decade)

1900	Karl Landsteiner discovers the A, B, and O blood groups.
1904.	Ivan Pavlov wins the Nobel Prize for his work on the physiology of digestion
1910	Sir Henry Dale describes properties of histamine.
1918	Earnest Starling describes how the force of the heart's contraction relates to the amount of blood in it.
1921	John Langley describes the functions of the autonomic nervous system.
1923	Sir Frederick Banting, Charles Best, and John Macleod win the Nobel Prize for the discovery of insulin
1932	Sir Charles Sherrington and Lord Edgar Adrian win the Nobel Prize for discoveries related to the functions of neurons.

1936	Sir Henry Dale and Otto Loewi win the Nobel Prize for the discovery of acetylcholine in synaptic transmission
1939–47	Albert von Szent-Györgyi explains the role of ATP and contributes to the understanding of actin and myosin in muscle contraction.
1949	Hans Selye discovers the common physiological responses to stress.
1953	Sir Hans Krebs wins the Nobel Prize for his discovery of the citric acid cycle.
1954	Hugh Huxley, Jean Hanson, R. Niedergerde, and Andrew Huxley propose the sliding filament theory of muscle contraction.
1962	Francis Crick, James Watson, and Maurice Wilkins win the Nobel Prize for determining the structure of DNA.
1963	Sir John Eccles, Sir Alan Hodgkin, and Sir Andrew Huxley win the Nobel Prize for their discoveries relating to the nerve impulse.
1971	Earl Sutherland wins the Nobel Prize for his discovery of the mechanism of hormone action.
1977	Roger Guillemin and Andrew Schally win the Nobel Prize for discoveries of the brain's production of peptide hormone.
1981	Roger Sperry wins the Nobel Prize for his discoveries regarding the specializations of the right and left cerebral hemispheres.
1986	Stanley Cohen and Rita Levi-Montalcini win the Nobel Prize for their discoveries of growth factors regulating the nervous system.
1994	Alfred Gilman and Martin Rodbell win the Nobel Prize for their discovery of the functions of G-proteins in signal transduction in cells.
1998	Robert Furchgott, Louis Ignarro, and Ferid Murad win the Nobel Prize for discovering the role of nitric oxide as a signaling molecule in the cardiovascular system.
2004	Linda B. Buck and Richard Axel win the Nobel Prize for their discoveries of odorant receptors and the organization of the olfactory system.
2006	Andrew Z. Fine and Craig C. Mello win the Noble Prize for their discovery of RNA interference by short, double-stranded RNA molecules.
2012	Sir John Gurdon and Shinya Yamanaka win the Nobel Prize for their discovery that mature cells can be reprogrammed to become pluripotent (like embryonic cells).

1.2. ORGANS AND SYSTEMS

LEARNING OUTCOMES

After studying this section, you should be able to:

Use the skin as an example to describe how the different primary tissues compose organs.

Identify the body fluid compartments.

Systems

Organs that are located in different regions of the body and that perform related functions are grouped into **systems.** These include the integumentary system, nervous system, endocrine system, skeletal system, muscular system, circulatory system, immune system, respiratory system, urinary system, alimentary (digestive) system, and reproductive system (table 1.1). By means of numerous regulatory mechanisms, these systems work together to maintain the life and health of the entire organism.

TABLE 1.1 | Organ Systems of the Body System

System	Major Organs or Tissues Primary	Functions
Circulatory	Heart, blood vessels, blood	Transport of blood throughout the body
Digestive	Mouth, salivary glands, pharynx, esophagus, stomach, small and large intestines, anus, pancreas, liver, gallbladder	Digestion and absorption of nutrients and water; elimination of wastes
Endocrine	adipose tissue, heart, and pineal gland; and endocrine cells in other organs	body, including growth, metabolism, reproduction, blood pressure, water and electrolyte balance, and others
Immune	White blood cells and their organs of production	Defense against pathogens
Integumentary	Skin	Protection against injury and dehydration; defense against pathogens; regulation of body temperature
Lymphatic	Lymph vessels, lymph nodes	Collection of extracellular fluid for return to blood participation in immune defenses; absorption of fats from digestive system
Musculoskeletal	Cartilage, bone, ligaments, tendons, joints, skeletal muscle	Support, protection, and movement of the body; production of blood cells
Nervous	Brain, spinal cord, peripheral nerves and ganglia, sense organs	Regulation and coordination of many activities in the body; detection of and response to changes in the internal and external environments; states of consciousness; learning; memory; emotion; others
Reproductive	Male:testes, penis, and associated ducts and glands Female: ovaries, fallopian tubes, uterus, vagina, mammary glands	Male: production of sperm; transfer of sperm to female Female: production of eggs; provision of a nutritive environment for the developing embryo and fetus; nutrition of the infant
Respiratory	Nose, pharynx, larynx, trachea, bronchi, lungs	Exchange of carbon dioxide and oxygen; regulation of hydrogen ion concentration in the body fluids
Urinary	Kidneys, ureters, bladder, urethra	Regulation of plasma composition through controlled excretion of ions, water, and organic wastes

Organs are composed of two or more primary tissues that serve the different functions of the organ. The skin is an organ that has numerous functions provided by its constituent tissues.

Or an **organ** is a structure composed of at least two, and usually all four, primary tissues. The largest organ in the body, in terms of surface area, is the skin (fig. 1.1). In this section, the numerous functions of the skin serve to illustrate how primary tissues cooperate in the service of organ physiology.

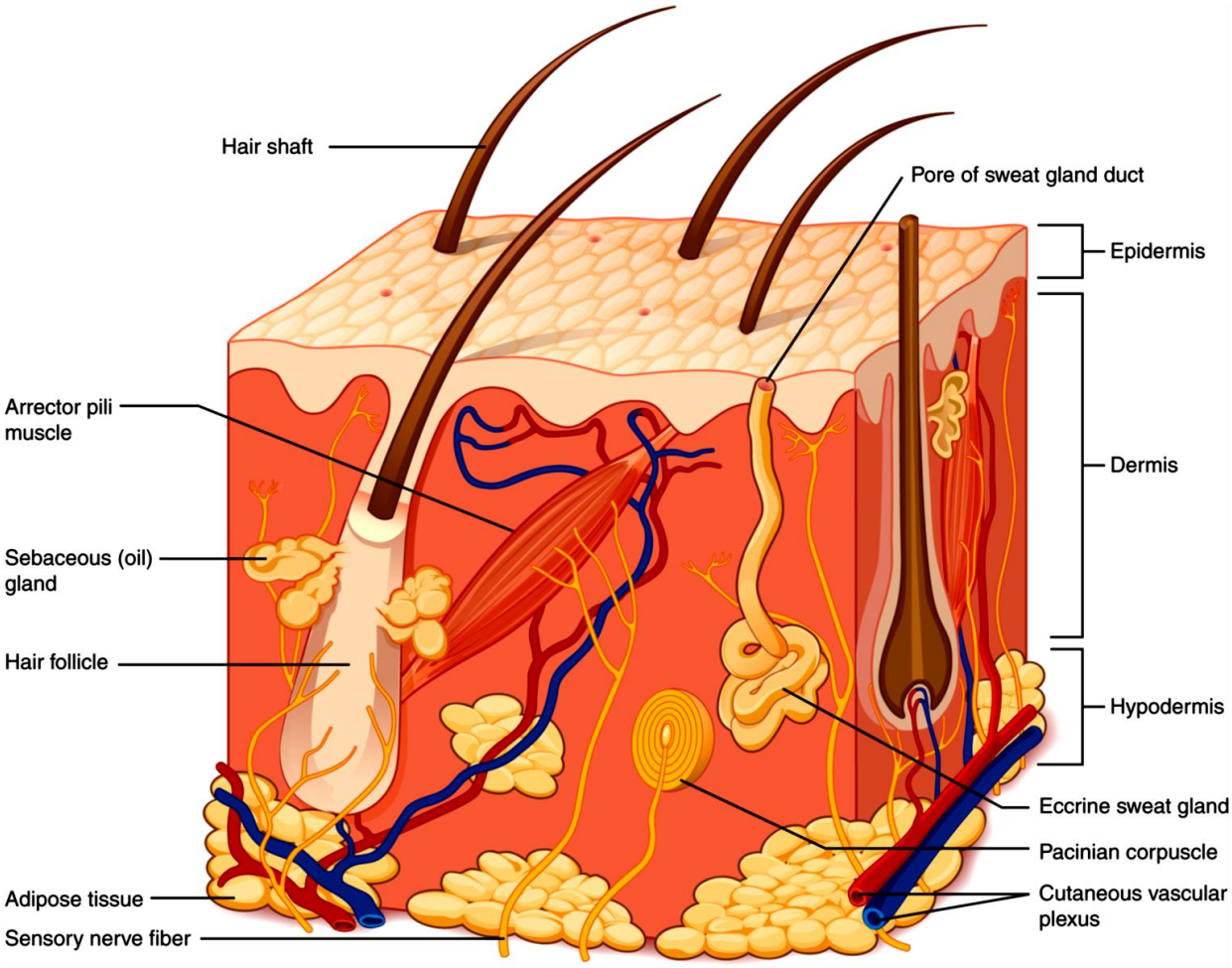

FIGURE 1. A diagram of the skin. The skin is an organ that contains all four types of primary tissues.

An Example of an Organ: The Skin

The confide *epidermis* protects the skin against water loss and against invasion by disease-causing organisms. Invaginations of the epithelium into the underlying connective tissue *dermis* create the exocrine glands of the skin. These include hair follicles (which produce the hair), sweat glands, and sebaceous glands. The secretion of sweat glands cools the body by evaporation and produces odors that, at least in lower animals, serve as sexual attractants. Sebaceous glands secrete oily sebum into hair follicles, which transport the sebum to the surface of the skin. Sebum lubricates the confide surface of the skin, helping to prevent it from drying and cracking.

The skin is nourished by blood vessels within the dermis. In addition to blood vessels, the dermis contains wandering white blood cells and other types of cells that protect against invading disease-causing organisms. It also contains nerve fibers and adipose (fat) cells; however, most of the adipose cells are grouped together to form the *hypodermis* (a layer beneath the dermis). Although adipose cells are a type of connective tissue, masses of fat deposits throughout the body are referred to as *adipose tissue.*

5.3 Functions of the Integumentary System

LEARNING OBJECTIVES

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

- Describe the different functions of the skin and the structures that enable them
- Explain how the skin helps maintain body temperature

The skin and accessory structures perform a variety of essential functions, such as protecting the body from invasion by microorganisms, chemicals, and other environmental factors; preventing dehydration; acting as a sensory organ; modulating body temperature and electrolyte balance; and synthesizing vitamin D. The underlying hypodermis has important roles in storing fats, forming a "cushion" over underlying structures, and providing insulation from cold temperatures.

Protection

The skin protects the rest of the body from the basic elements of nature such as wind, water, and UV sunlight. It acts as a protective barrier against water loss, due to the presence of layers of keratin and glycolipids in the stratum corneum. It also is the first line of defense against abrasive activity due to contact with grit, microbes, or harmful chemicals. Sweat excreted from sweat glands deters microbes from over-colonizing the skin surface by generating dermicidin, which has antibiotic properties.

The color of skin is influenced by a number of pigments, including melanin, carotene, and hemoglobin. Melanin is produced by cells called melanocytes, which are found scattered throughout the stratum basal of the epidermis. The melanin is transferred into the keratinocytes via a cellular vesicle called a **melanosome ,** which have role in protect from UV.

Sensory Function

The fact that you can feel an ant crawling on your skin, allowing you to flick it off before it bites, is because the skin, and especially the hairs projecting from hair follicles in the skin, can sense changes in the environment. The hair root plexus surrounding the base of the hair follicle senses a disturbance, and then transmits the information to the central nervous system (brain and spinal cord), which can then respond by activating the skeletal muscles of your eyes to see the ant and the skeletal muscles of the body to act against the ant.

The skin acts as a sense organ because the epidermis, dermis, and the hypodermis contain specialized sensory nerve structures that detect touch, surface temperature, and pain. These receptors are more concentrated on the tips of the fingers, which are most sensitive to touch, especially the **Meissner corpuscle** (tactile corpuscle) (Figure 1), which responds to light touch, and the **Pacinian corpuscle** (lamellated corpuscle), which responds to vibration. Merkel cells, seen scattered in the stratum basale, are also touch receptors. In addition to these specialized receptors, there are sensory nerves connected to each hair follicle, pain and temperature receptors scattered throughout the skin, and motor nerves

innervate the arrector pili muscles and glands. This rich innervation helps us sense our environment and react accordingly.

Thermoregulation

The integumentary system helps regulate body temperature through its tight association with the sympathetic nervous system, the division of the nervous system involved in our fight-or-flight responses. The sympathetic nervous system is continuously monitoring body temperature and initiating appropriate motor responses. Recall that sweat glands, accessory structures to the skin, secrete water, salt, and other substances to cool the body when it becomes warm. Even when the body does not appear to be noticeably sweating, approximately 500 mL of sweat (insensible perspiration) are secreted a day. If the body becomes excessively warm due to high temperatures, vigorous activity, or a combination of the two, sweat glands will be stimulated by the sympathetic nervous system to produce large amounts of sweat, as much as 0.7 to 1.5 L per hour for an active person. When the sweat evaporates from the skin surface, the body is cooled as body heat is dissipated.

In addition to sweating, arterioles in the dermis dilate so that excess heat carried by the blood can dissipate through the skin and into the surrounding environment. This accounts for the skin redness that many people experience when exercising.

When body temperatures drop, the arterioles constrict to minimize heat loss, particularly in the ends of the digits and tip of the nose. This reduced circulation can result in the skin taking on a whitish hue. Although the temperature of the skin drops as a result, passive heat loss is prevented, and internal organs and structures remain warm. If the temperature of the skin drops too much (such as environmental temperatures below freezing), the conservation of body core heat can result in the skin actually freezing, a condition called frostbite.

Vitamin D Synthesis

The epidermal layer of human skin synthesizes **vitamin D** when exposed to UV radiation. In the presence of sunlight, a form of vitamin D3 called cholecalciferol is synthesized from a derivative of the steroid cholesterol in the skin. The liver converts cholecalciferol to calcidiol, which is then converted to calcitriol (the active chemical form of the vitamin) in the kidneys. Vitamin D is essential for normal absorption of calcium and phosphorous, which are required for healthy bones. The absence of sun exposure can lead to a lack of vitamin D in the body, leading to a condition called **rickets**, a painful condition in children where the bones are misshapen due to a lack of calcium, causing bowleggedness. Elderly individuals who suffer from vitamin D deficiency can develop a condition called osteomalacia, a softening of the bones. In present day society, vitamin D is added as a supplement to many foods, including milk and orange juice, compensating for the need for sun exposure. In addition to its essential role in bone health,

vitamin D is essential for general immunity against bacterial, viral, and fungal infections. Recent studies are also finding a link between insufficient vitamin D and cancer.

Body Fluid Compartments

Another useful way to think about how the body is organized is to consider body fluid compartments. When we refer to "body fluid," we are referring to a watery solution of dissolved substances such as oxygen, nutrients, and wastes.

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 2).

Intracellular fluid is the fluid contained within all the cells of the body and accounts for about 67% of all the fluid in the body. Collectively, the fluid present in the blood and in the spaces surrounding cells is called **extracellular fluid,** that is, all the fluid that is outside of cells. Of this, only about 20%–25% is in the fluid portion of blood, which is called the **plasma,** in which the various blood cells are suspended. The remaining 75%–80% of the extracellular fluid, which lies around and between cells, is known as the **interstitial fluid.** The space containing interstitial fluid is called the **interstitium.** Therefore, the total volume of extracellular fluid is the sum of the plasma and interstitial fluid volumes.

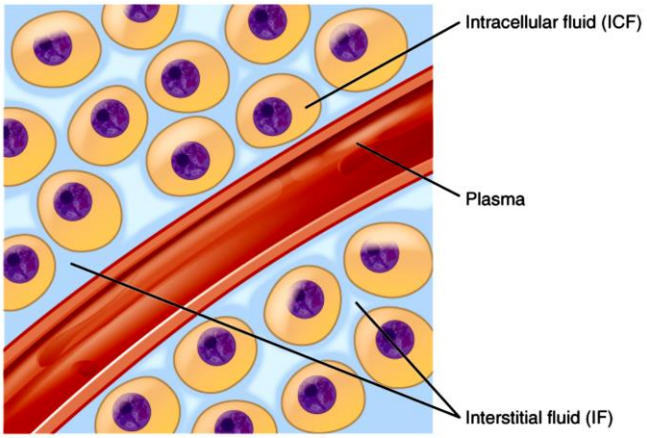

FIGURE 2. Fluid Compartments in the Human Body The intracellular fluid (ICF) is the fluid within cells. The interstitial fluid (IF) is part of the extracellular fluid (ECF) between the cells. Blood plasma is the second part of the ECF. Materials travel between cells and the plasma in capillaries through 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. 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.

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 THE BLOOD

LEARNING OUTCOMES

After studying this section, you will be able to:

- Identify the primary functions of blood, its fluid and cellular components, and its physical characteristics
- Identify the most important proteins and other solutes present in blood plasma
- Describe the formation of the formed element components of blood
- Discuss the structure and function of red blood cells and hemoglobin
- Classify and characterize white blood cells
- Describe the structure of platelets and explain the process of hemostasis
- Explain the significance of AB and Rh blood groups in blood transfusions
- Discuss a variety of blood disorders

Single-celled organisms do not need blood. They obtain nutrients directly from and excrete wastes directly into their environment. The human organism cannot do that. Our large, complex bodies need blood to deliver nutrients to and remove wastes from our trillions of cells. The heart pumps blood = throughout the body in a network of blood vessels. Together, these three components−blood, heart, and vessels−makes up the cardiovascular system. This section focuses on the medium of transport: blood.

Blood consists of formed elements that are suspended and carried in a fluid called plasma. The formed elements—erythrocytes, leukocytes, and platelets—function respectively in oxygen transport, immune defense, and blood clotting.

An Overview of Blood

LEARNING OBJECTIVES

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

- Identify the primary functions of blood in transportation, defense, and maintenance of homeostasis
- Name the fluid component of blood and the three major types of formed elements, and identify their relative proportions in a blood sample
- Discuss the unique physical characteristics of blood
- Identify the composition of blood plasma, including its most important solutes and plasma proteins

Recall that **blood** is a connective tissue. Like all connective tissues, it is made up of cellular elements and an. extracellular matrix. The cellular elements—referred to as the **formed elements**—include **red blood cells (RBCs)**, **white blood cells (WBCs)**, and cell fragments called **platelets**. The extracellular matrix, called **plasma**, makes blood unique among connective tissues because it is fluid. This fluid, which is mostly water, perpetually suspends the formed elements and enables them to circulate throughout the body within the cardiovascular system.

Functions of Blood

The primary function of blood is to deliver oxygen and nutrients to and remove wastes from body cells, but that is only the beginning of the story. The specific functions of blood also include defense, distribution of heat, and maintenance of homeostasis.

Transportation

Nutrients from the foods you eat are absorbed in the digestive tract. Most of these travel in the bloodstream directly to the liver, where they are processed and released back into the bloodstream for delivery to body cells. Oxygen from the air you breathe diffuses into the blood, which moves from the lungs to the heart, which then pumps it out to the rest of the body. Moreover, endocrine glands scattered throughout the body release their products, called hormones, into the bloodstream, which carries them to distant target cells. Blood also picks up cellular wastes and byproducts, and transports them to various organs for removal. For instance, blood moves carbon dioxide to the lungs for exhalation from the body, and various waste products are transported to the kidneys and liver for excretion from the body in the form of urine or bile.

Defense

Many types of WBCs protect the body from external threats, such as disease-causing bacteria that have entered the bloodstream in a wound. Other WBCs seek out and destroy internal threats, such as cells with mutated DNA that could multiply to become cancerous, or body cells infected with viruses.

When damage to the vessels results in bleeding, blood platelets and certain proteins dissolved in the plasma, the fluid portion of the blood, interact to block the ruptured areas of the blood vessels involved. This protects the body from further blood loss.

Maintenance of Homeostasis

Recall that body temperature is regulated via a classic negative-feedback loop. If you were exercising on a warm day, your rising core body temperature would trigger several homeostatic mechanisms, including increased transport of blood from your core to your body periphery, which is typically cooler. As blood passes through the vessels of the skin, heat would be dissipated to the environment, and the blood returning to your body core would be cooler. In contrast, on a cold day, blood is diverted away from the skin to maintain a warmer body core. In extreme cases, this may result in frostbite.

Blood also helps to maintain the chemical balance of the body. Proteins and other compounds in blood act as buffers, which thereby help to regulate the pH of body tissues. Blood also helps to regulate the water content of body cells.

Composition of Blood

You have probably had blood drawn from a superficial vein in your arm, which was then sent to a lab for analysis. Some of the most common blood tests—for instance, those measuring lipid or glucose levels in plasma—determine which substances are present within blood and in what quantities. Other blood tests check for the composition of the blood itself, including the quantities and types of formed elements. One such test, called a **hematocrit**, measures the percentage of RBCs, clinically known as erythrocytes, in a blood sample. It is performed by spinning the blood sample in a specialized centrifuge, a process that causes the heavier elements suspended within the blood sample to separate from the lightweight, liquid plasma (Figure 4 ; 5). Because the heaviest elements in blood are the erythrocytes, these settle at the very bottom of the hematocrit tube. Located above the erythrocytes is a pale, thin layer composed of the remaining formed elements of blood. These are the

WBCs, clinically known as leukocytes, and the platelets, cell fragments also called thrombocytes. This layer is referred to as the **buffy coat** because of its color; it normally constitutes less than 1 percent of a blood sample. Above the buffy coat is the blood plasma, normally a pale, straw-colored fluid, which constitutes the remainder of the sample.

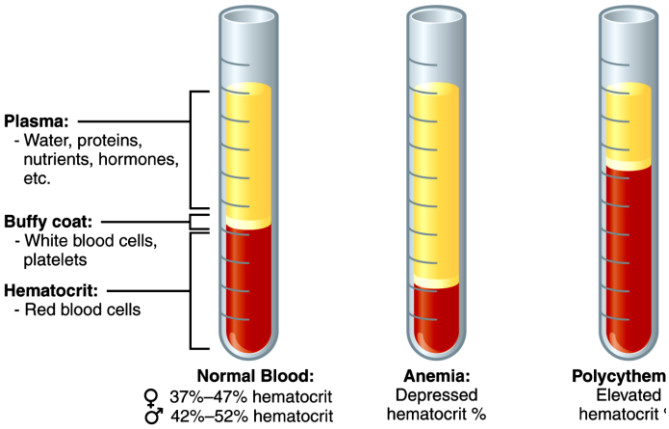

FIGURE.4 Composition of Blood The cellular elements of blood include a vast number of erythrocytes and comparatively fewer leukocytes and platelets. Plasma is the fluid in which the formed elements are suspended. A sample of blood spun in a centrifuge reveals that plasma is the lightest component. It floats at the top of the tube separated from the heaviest elements, the erythrocytes, by a buffy coat of leukocytes and platelets. Hematocrit is the percentage of the total sample that is comprised of erythrocytes. Depressed and elevated hematocrit levels are shown for comparison

Blood Plasma

Blood plasma is a straw-colored liquid consisting of water and dissolved solutes. The major solute of the plasma in terms of its concentration is Na^+. In addition to Na^+, plasma contains many other ions, as well as organic molecules such as metabolites, hormones, enzymes, antibodies, and other proteins. The concentrations of some of these plasma constituents are shown in table 1.

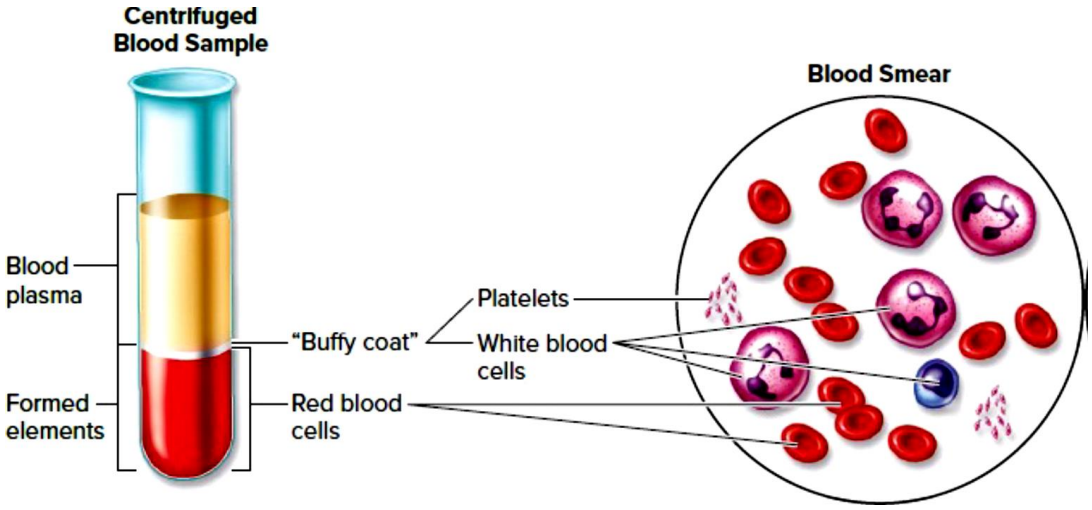

FIGURE 5. The constituents of blood. Blood cells become packed at the bottom of the test tube when whole blood is centrifuged, leaving the blood plasma at the top of the tube. Red blood cells are the most abundant of the blood cells—white blood cells and platelets form only a thin, light-colored "buffy coat" at the interface between the packed red blood cells and the plasma.

TABLE 1 | Representative Normal Blood Values

Measurement	Normal Range
Blood volume	80–85 ml/kg body weight
Blood osmolality	285–295 mOsm
Blood pH	7.38–7.44
Enzymes	
Creatine phosphokinase (CPK)	Female: 10–79 U/L
	Male: 17–148 U/L
Lactic dehydrogenase	(LDH) 45–90 U/L

Phosphatase (acid)	Female: 0.01–0.56 Sigma U/ml
	Male: 0.13–0.63 Sigma U/ml
Hematology Values	
Hematocrit	Female: 36%–46%
	Male: 41%–53%
Hemoglobin	
	Female: 12-16 g/100 ml
	Male: 13.5-17.5 g/100 ml
Red blood cell count	4.50-5.90 million/mm3
White blood cell count	4,500-11,000/mm3
Hormones	
Testosterone	Male: 270-1,070 ng/100 ml Female: 6-86 ng/100 ml
Adrenocorticotropic hormone (ACTH)	6-76 pg/ml
Growth hormone	Children: over 10 ng/ml
	Adult male: below 5 ng/ml
Insulin	2-20 μ U/ml (fasting)
Ions	
Bicarbonate	24-30 mmol/l
Calcium	9.0-10.5 mg/dl
Chloride	98-106 mEq/L
Potassium	3.5-5.0 mEq/L
Sodium	135-145 mEq/L
Organic Molecules (Other)	
Cholesterol, desirable	under 200 mg/dl
Glucose	75-115 mg/dl (fasting)
Lactic acid	5-15 mg/dl
Protein (total)	5.5-8.0 g/dl
Triglyceride	under 160 mg/dl
Urea nitrogen	10-20 mg/dl
Uric acid	Male: 2.5-8.0 mg/dl
	Female: 1.5-6.0 mg/dl

The Formed Elements of Blood

The **formed elements** of blood include two types of complete blood cells: *erythrocytes*, or *red blood cells*, and *leukocytes*, or *white blood cells* (table 2). Erythrocytes are by far the more numerous of the two. A cubic millimeter of blood normally contains 5.1 million to 5.8 million erythrocytes in males and

4.3 million to 5.2 million erythrocytes in females. By contrast, the same volume of blood contains only 5,000 to 9,000 leukocytes.

Erythrocytes

Erythrocytes are flattened, biconcave discs about 7 μm in diameter and 2.2 μm thick. Their unique shape relates to their function of transporting oxygen; it provides an increased surface area through which gas can diffuse (figure. 6).

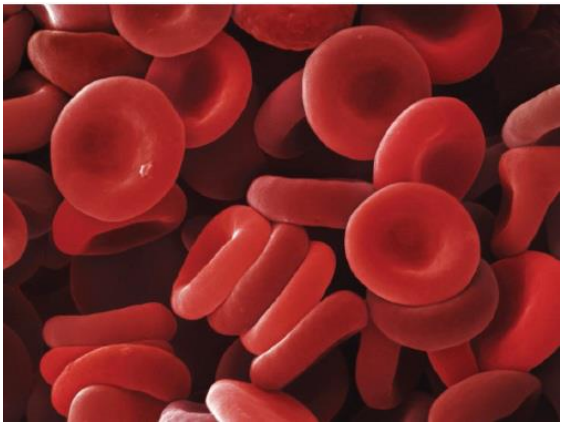

FIGURE 6 A colorized scanning electron micrograph of red blood cells. The shape of the red blood cells is described as a "biconcave disc." In reality, individual red blood cells do not look red when viewed under a microscope.

Table 2. Major Blood Components

Component and % of blood	Subcomponent and % of component	Type and % (where appropriate)	Site of production	Major function(s)
Plasma 46–63 percent	Water 92 percent	Fluid	Absorbed by intestinal tract or produced by metabolism	Transport medium
	Plasma proteins 7 percent	Albumin 54–60 percent	Liver	Maintain osmotic concentration, transport lipid molecules
		Globulins 35–38 percent	Alpha globulins—liver	Transport, maintain osmotic concentration
			Beta globulins—liver	Transport, maintain osmotic concentration
			Gamma globulins (immunoglobulins)—plasma cells	Immune responses
		Fibrinogen 4–7 percent	Liver	Blood clotting in hemostasis
	Regulatory proteins <1 percent	Hormones and enzymes	Various sources	Regulate various body functions
	Other solutes 1 percent	Nutrients, gases, and wastes	Absorbed by intestinal tract, exchanged in respiratory system, or produced by cells	Numerous and varied
Formed elements 37–54 percent	Erythrocytes 99 percent	Erythrocytes	Red bone marrow	Transport gases, primarily oxygen and some carbon dioxide
	Leukocytes <1 percent Platelets <1 percent	Granular leukocytes: neutrophils eosinophils basophils	Red bone marrow	Nonspecific immunity
		Agranular leukocytes: lymphocytes monocytes	Lymphocytes: bone marrow and lymphatic tissue	Lymphocytes: specific immunity
			Monocytes: red bone marrow	Monocytes: nonspecific immunity
	Platelets <1 percent		Megakaryocytes: red bone marrow	Hemostasis

Erythrocytes lack nuclei and mitochondria (they obtain energy through anaerobic metabolism). Partly because of these deficiencies, erythrocytes have a relatively short circulating life span of only about 120 days. Older erythrocytes are removed from the circulation by phagocytic cells in the liver, spleen, and bone marrow.

Each erythrocyte contains approximately 280 million **hemoglobin** molecules, which give blood its red color. Each hemoglobin molecule consists of four protein chains called *globins*, each of which is bound to one *heme*, a red pigmented molecule that contains iron. The iron group of heme is able to combine with oxygen in the lungs and release oxygen in the tissues.

The heme iron is recycled from senescent (old) red blood cells by phagocytes in the liver and spleen. This iron travels in the blood to the bone marrow attached to a protein carrier called **transferrin,** which enters the erythrocytes by receptor-mediated endocytosis. This recycled heme iron supplies most of the body' s need for iron. Additionally, iron can be released from where it is stored within the hepatocytes of the liver. The balance of the requirement for iron, though relatively small, must be made up for in the diet. Dietary iron is absorbed mostly in the duodenum (the first part of the small intestine) and transported from the intestine bound to transferrin in the blood.

The transferrin with its bound iron is taken out of the blood by cells of the bone marrow and liver by endocytosis, which is triggered by binding of transferrin to its membrane receptors. Although the bone marrow produces about 200 billion red blood cells each day, and erythrocytes contain about 2 to 3 g of iron, we normally need only a small amount of iron in the diet to compensate for the small amount lost from the body. However, if there is a dietary iron deficiency that reduces the ability of the bone marrow to produce hemoglobin, an ***iron-deficiency anemia*** may result.

Anemia can also result from a deficiency in vitamin B12 due to lack of a stomach secretion called ***intrinsic factor***

Leukocytes

Leukocytes differ from erythrocytes in several respects. Leukocytes contain nuclei and mitochondria and can move in an amoeboid fashion. Because of their amoeboid ability, leukocytes can squeeze through pores in capillary walls and move to a site of infection, whereas erythrocytes usually remain confined within blood vessels. The movement of leukocytes through capillary walls is referred to as *diapedesis* or *extravasation.*

White blood cells are almost invisible under the microscope unless they are stained; therefore, they are classified according to their staining properties. Those leukocytes that have granules in their cytoplasm are called **granular leukocytes** (or *granulocytes*); those without clearly visible granules are called **agranular leukocytes** (or *agranulocytes*).

The stain used to identify white blood cells is usually a mixture of a pink-tored stain called *eosin* and a blue-to-purple stain (methylene blue), which is called a "basic stain." Granular leukocytes with red-staining granules are therefore called **eosinophils,** and those with blue-staining granules are called **basophils.** Those with granules that have little affinity for either stain are **neutrophils** (figure 7). Neutrophils are the most abundant type of leukocyte, accounting for 50% to 70% of the leukocytes in the blood. Immature neutrophils have sausage shaped. nuclei and are called *band cells.* As the band cells

mature, their nuclei become lobulated, with two to five lobes connected by thin strands. At this stage, the neutrophils are also known as *polymorphonuclear leukocytes (PMNs).* There are two types of agranular leukocytes: lymphocytes and monocytes.

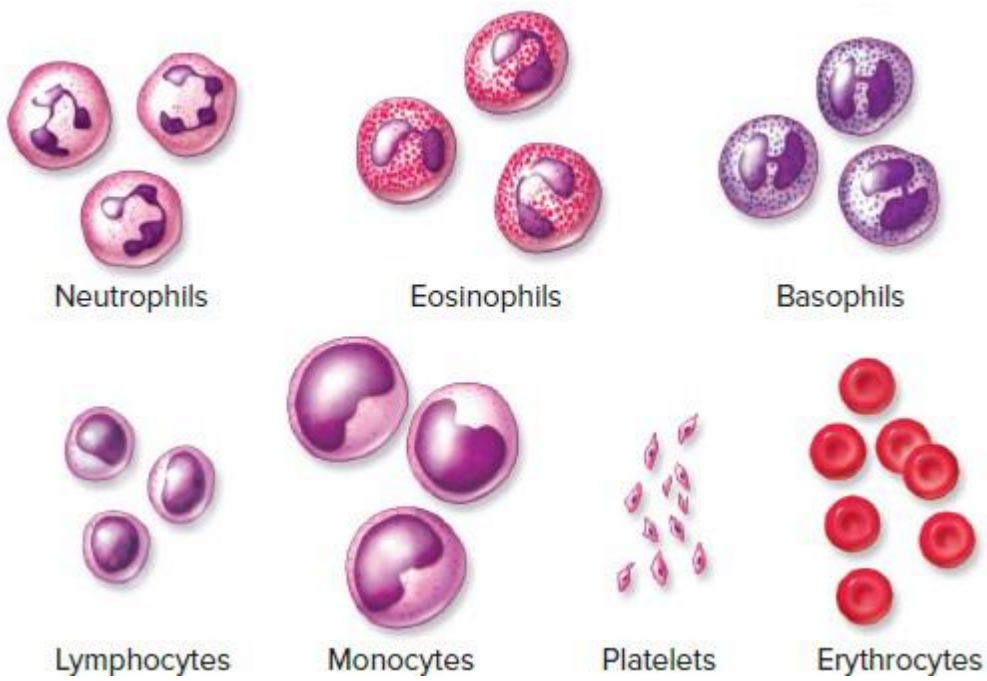

FIGURE 7. The blood cells and platelets. The white blood cells depicted above are granular leukocytes, and are named according to their affinity for stain. The lymphocytes and monocytes shown below are agranular leukocytes.

Lymphocytes are usually the second most numerous type of leukocyte; they are small cells with round nuclei and little cytoplasm. **Monocytes,** by contrast, are the largest of the leukocytes and generally have kidney- or horseshoe-shaped nuclei. In addition to these two cell types, there are smaller numbers of *plasma cells,* which are derived from lymphocytes. Plasma cells produce and secrete large amounts of antibodies.

Platelets

Platelets, or **thrombocytes,** are the smallest of the formed elements and are actually fragments of large cells called *megakaryocytes,* which are found in bone marrow. (This is why the term *formed elements* is used instead of *blood cells* to describe erythrocytes, leukocytes, and platelets.) The fragments that enter the circulation as platelets lack nuclei but, like leukocytes, are capable of amoeboid movement. The platelet count per cubic millimeter of blood ranges from 130,000 to 400,000, and this count can vary

greatly under different physiological conditions. Platelets survive for about five to nine days before being destroyed by the spleen and liver.

Platelets play an important role in blood clotting. They constitute most of the mass of the clot, and phospholipids in their plasma membranes activate the clotting factors in plasma that result in threads of fibrin, which reinforce the platelet plug. Platelets that attach together in a blood clot release *serotonin*, a chemical that stimulates constriction of blood vessels, thus reducing the flow of blood to the injured area. Platelets also secrete growth factors (autocrine regulators), which are important in maintaining the integrity of blood vessels.

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LEARNING OBJECTIVES

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

- Describe the three mechanisms involved in hemostasis
- Explain how the extrinsic and intrinsic coagulation pathways lead to the common pathway, and the coagulation factors involved in each

Blood Clotting

When a blood vessel is injured, a number of physiological mechanisms are activated that promote **hemostasis,** or the cessation of bleeding (*hemo* = blood; *stasis* = standing). Breakage of the endothelial lining of a vessel exposes collagen proteins from the sub-endothelial connective tissue to the blood. This initiates three separate, but overlapping, hemostatic mechanisms: (1) vasoconstriction, (2) the formation of a platelet plug, and (3) the production of a web of fibrin proteins that penetrates and surrounds the platelet plug.

Vascular Spasm (vasoconstriction)

When a vessel is severed or punctured, or when the wall of a vessel is damaged, vascular spasm occurs. In **vascular spasm**, the smooth muscle in the walls of the vessel contracts dramatically. This smooth muscle has both circular layers; larger vessels also have longitudinal layers. The circular layers tend to constrict the flow of blood, whereas the longitudinal layers, when present, draw the vessel back into the surrounding tissue, often making it more difficult for a surgeon to locate, clamp, and tie off a severed vessel. The vascular spasm response is believed to be triggered by several chemicals called endothelins that are released by vessel-lining cells and by pain receptors in response to vessel injury. This phenomenon typically lasts for up to 30 minutes, although it can last for hours.

In addition, the endothelial cells secrete *prostacyclin* (or *PGI*2, a type of prostaglandin and *nitric oxide* (*NO*), which (1) act as vasodilators and (2) act on the platelets to inhibit platelet aggregation. In addition, the plasma membrane of endothelial cells contains an enzyme known as *CD39*, which has its active site facing the blood. The CD39 enzyme breaks down ADP in the blood to AMP and P*i* (ADP is released by activated platelets and promotes platelet aggregation, as described shortly).

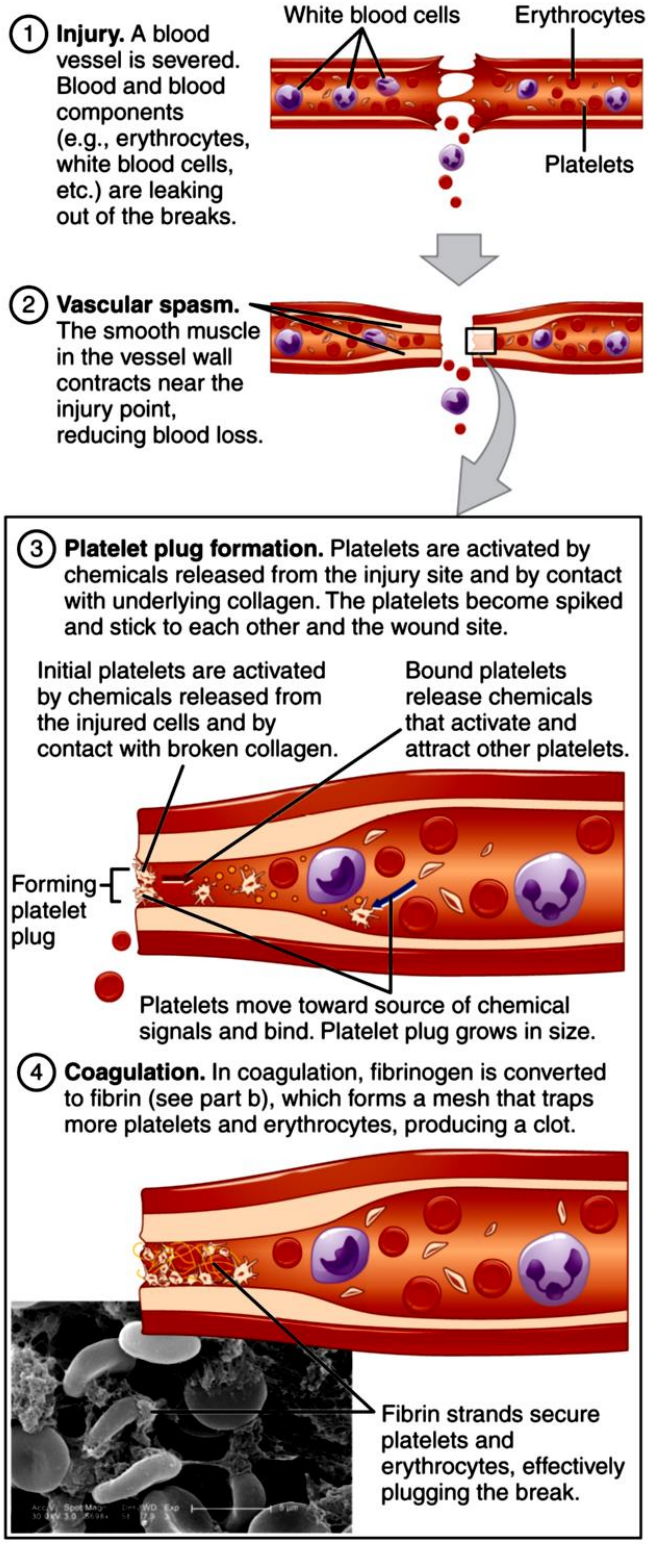

FIGURE 18.14 Hemostasis (a) An injury to a blood vessel initiates the process of hemostasis. Blood clotting involves three steps. First, vascular spasm constricts the flow of blood. Next, a platelet plug forms to temporarily seal small openings in the vessel. Coagulation then enables the repair of the vessel wall once the leakage of blood has stopped. (b) The synthesis of fibrin in blood clots involves either an intrinsic pathway or an extrinsic pathway, both of which lead to a common pathway.

Formation of the Platelet Plug

In the second step, platelets, which normally float free in the plasma, encounter the area of vessel rupture with the exposed underlying connective tissue and collagenous fibers. The platelets begin to clump together, become spiked and sticky, and bind to the exposed collagen and endothelial lining. This process is assisted by a glycoprotein in the blood plasma called von Willebrand factor, which helps stabilize the growing **platelet plug**. As platelets collect, they simultaneously release chemicals from their granules into the plasma that further contribute to hemostasis. Among the substances released by the platelets are:

• adenosine diphosphate (ADP), which helps additional platelets to adhere to the injury site, reinforcing and expanding the platelet plug
• serotonin, which maintains vasoconstriction
• prostaglandins and phospholipids, which also maintain vasoconstriction and help to activate further clotting chemicals

Platelets contain secretory granules; when platelets stick to collagen, they *degranulate* as the secretory granules release their products. These products include *adenosine diphosphate (ADP), serotonin,* and a prostaglandin called *thromboxane A*2. This event is known as the **platelet release reaction.** The ADP and thromboxane A2 released from activated platelets recruits new platelets to the vicinity and makes them "sticky" so that they adhere to those stuck on the collagen.

A platelet plug can temporarily seal a small opening in a blood vessel. Plug formation, in essence, buys the body time while more sophisticated and durable repairs are being made. In a similar manner, even modern naval warships still carry an assortment of wooden plugs to temporarily repair small breaches in their hulls until permanent repairs can be made.

Coagulation

Those more sophisticated and more durable repairs are collectively called **coagulation**, the formation of a blood clot. The process is sometimes characterized as a cascade, because one event prompts the next as in a multi-level waterfall. The result is the production of a gelatinous but robust clot made up of a mesh of **fibrin**—an insoluble filamentous protein derived from fibrinogen, the plasma protein introduced earlier—in which platelets and blood cells are trapped. Figure 1 summarizes the three steps of hemostasis.

Clotting Factors Involved in Coagulation

In the coagulation cascade, chemicals called **clotting factors** (or coagulation factors) prompt reactions that activate still more coagulation factors. The process is complex, but is initiated along two basic pathways:

· The extrinsic pathway, which normally is triggered by trauma. The extrinsic pathway of clot formation is initiated by **tissue factor** (or *tissue thromboplastin*, also known as *factor III*), a membrane glycoprotein found inside the walls of blood vessels (in the tunica media and tunica externa; and the cells of the surrounding tissues.

Table 1 clotting factors

Factor number	Name	Type of molecule	Source	Pathway(s)
I	Fibrinogen	Plasma protein	Liver	Common; converted into fibrin
II	Prothrombin	Plasma protein	Liver*	Common; converted into thrombin
III	Tissue thromboplastin or tissue factor	Lipoprotein mixture	Damaged cells and platelets	Extrinsic
IV	Calcium ions	Inorganic ions in plasma	Diet, platelets, bone matrix	Entire process
V	Proaccelerin	Plasma protein	Liver, platelets	Extrinsic and intrinsic
VI	Not used	Not used	Not used	Not used
VII	Proconvertin	Plasma protein	Liver *	Extrinsic
VIII	Antihemolytic factor A	Plasma protein factor	Platelets and endothelial cells	Intrinsic; deficiency results in hemophilia A
IX	Antihemolytic factor B (plasma thromboplastin component)	Plasma protein	Liver*	Intrinsic; deficiency results in hemophilia B
X	Stuart–Prower factor (thrombokinase)	Protein	Liver*	Extrinsic and intrinsic
XI	Antihemolytic factor C (plasma thromboplastin antecedent)	Plasma protein	Liver	Intrinsic; deficiency results in hemophilia C
XII	Hageman factor	Plasma protein	Liver	Intrinsic; initiates clotting in vitro also activates plasmin
XIII	Fibrin-stabilizing factor	Plasma protein	Liver, platelets	Stabilizes fibrin; slows fibrinolysis

· The intrinsic pathway, which begins in the bloodstream and is triggered by internal damage to the wall of the Both of these merge into a third pathway, referred to as the common pathway (see Figure 1 **b**). All three pathways are dependent upon the 12 known clotting factors, including Ca2+ and vitamin K (Table 1). Clotting factors are secreted primarily by the liver and the platelets. The liver requires the fat-soluble vitamin K to produce many of them. Vitamin K (along with biotin and folate) is somewhat unusual among vitamins in that it is not only consumed in the diet but is also synthesized by bacteria residing in the large intestine. The calcium ion, considered factor IV, is derived from the diet and from the

breakdown of bone. Some recent evidence indicates that activation of various clotting factors occurs on specific receptor sites on the surfaces of platelets.

The 12 clotting factors are numbered I through XIII according to the order of their discovery. Factor VI was once believed to be a distinct clotting factor, but is now thought to be identical to factor V. Rather than renumber the other factors, factor VI was allowed to remain as a placeholder and also a reminder that knowledge changes over time.

Disorders of Clotting

Either an insufficient or an excessive production of platelets can lead to severe disease or death. As discussed earlier, an insufficient number of platelets, called thrombocytopenia, typically results in the inability of blood to form clots. This can lead to excessive bleeding, even from minor wounds.

Another reason for failure of the blood to clot is the inadequate production of functional amounts of one or more clotting factors. This is the case in the genetic disorder **hemophilia**, which is actually a group of related disorders, the most common of which is hemophilia A, accounting for approximately 80 percent of cases. This disorder results in the inability to synthesize sufficient quantities of factor VIII. Hemophilia B is the second most common form, accounting for approximately 20 percent of cases. In this case, there is a deficiency of factor IX. Both of these defects are linked to the X chromosome and are typically passed from a healthy (carrier) female to their male offspring, since males are XY. Females would need to inherit a defective gene from each parent to manifest the disease, since they are XX. Patients with hemophilia bleed from even minor internal and external wounds, and leak blood into joint spaces after exercise and into urine and stool. Hemophilia C is a rare condition that is triggered by an autosomal (not sex) chromosome that renders factor XI nonfunctional. It is not a true recessive condition, since even individuals with a single copy of the mutant gene show a tendency to bleed. Regular infusions of clotting factors isolated from healthy donors can help prevent bleeding in hemophiliac patients. At some point, genetic therapy will become a viable option.

In contrast to the disorders characterized by coagulation failure is thrombocytosis, also mentioned earlier, a condition characterized by excessive numbers of platelets that increases the risk for excessive clot formation, a condition known as **thrombosis**. A **thrombus** (plural = thrombi) is an aggregation of platelets, erythrocytes, and even WBCs typically trapped within a mass of fibrin strands. While the formation of a clot is normal following the hemostatic mechanism just described, thrombi can form within an intact or only slightly damaged blood vessel. In a large vessel, a thrombus will adhere to the vessel wall and decrease the flow of blood, and is referred to as a mural thrombus. In a small vessel, it may actually totally block the flow of blood and is termed an occlusive thrombus.

Thrombi are most commonly caused by vessel damage to the endothelial lining, which activates the clotting mechanism. These may include venous stasis, when blood in the veins, particularly in the legs,

remains stationary for long periods. This is one of the dangers of long airplane flights in crowded conditions and may lead to deep vein thrombosis. Thrombophilia, also called hypercoagulation, is a condition in which there is a tendency to form thrombosis. This may be familial (genetic) or acquired. Acquired forms include the autoimmune disease lupus, immune reactions to heparin, polycythemia vera, thrombocytosis, sickle cell disease, pregnancy, and even obesity. A thrombus can seriously impede blood flow to or from a region and will cause a local increase in blood pressure. If flow is to be maintained, the heart will need to generate a greater pressure to overcome the resistance.

When a portion of a thrombus breaks free from the vessel wall and enters the circulation, it is referred to as an **embolus**. An embolus that is carried through the bloodstream can be large enough to block a vessel critical to a major organ. When it becomes trapped, an embolus is called an embolism. In the heart, brain, or lungs, an embolism may accordingly cause a heart attack, a stroke, or a pulmonary embolism. These are medical emergencies.

Among the many known biochemical activities of aspirin is its role as an anticoagulant. Aspirin (acetylsalicylic acid) is very effective at inhibiting the aggregation of platelets. It is routinely administered during a heart attack or stroke to reduce the adverse effects. Physicians sometimes recommend that patients at risk for cardiovascular disease take a low dose of aspirin on a daily basis as a preventive measure. However, aspirin can also lead to serious side effects, including increasing the risk of ulcers. A patient is well advised to consult a physician before beginning any aspirin regimen.

A class of drugs collectively known as thrombolytic agents can help speed up the degradation of an abnormal clot. If a thrombolytic agent is administered to a patient within 3 hours following a thrombotic stroke, the patient’s prognosis improves significantly. However, some strokes are not caused by thrombi, but by hemorrhage. Thus, the cause must be determined before treatment begins. Tissue plasminogen activator is an enzyme that catalyzes the conversion of plasminogen to plasmin, the primary enzyme that breaks down clots. It is released naturally by endothelial cells but is also used in clinical medicine. New research is progressing using compounds isolated from the venom of some species of snakes, particularly vipers and cobras, which may eventually have therapeutic value as thrombolytic agents.

Plasma Proteins

About 7 percent of the volume of plasma—nearly all that is not water—is made of proteins. These include several plasma proteins (proteins that are unique to the plasma), plus a much smaller number of regulatory proteins, including enzymes and some hormones.

The three major groups of plasma proteins are as follows:

• **Albumin** is the most abundant of the plasma proteins. Manufactured by the liver, albumin molecules serve as binding proteins—transport vehicles for fatty acids and steroid hormones. Recall that lipids are

hydrophobic; however, their binding to albumin enables their transport in the watery plasma. Albumin is also the most significant contributor to the osmotic pressure of blood; that is, its presence holds water inside the blood vessels and draws water from the tissues, across blood vessel walls, and into the bloodstream. This in turn helps to maintain both blood volume and blood pressure. Albumin normally accounts for approximately 54 percent of the total plasma protein content, in clinical levels of 3.5–5.0 g/dL blood.

• The second most common plasma proteins are the **globulins**. A heterogeneous group, there are three main subgroups known as alpha, beta, and gamma globulins. The alpha and beta globulins transport iron, lipids, and the fat-soluble vitamins A, D, E, and K to the cells; like albumin, they also contribute to osmotic pressure. The gamma globulins are proteins involved in immunity and are better known as an **antibodies** or **immunoglobulins**. Although other plasma proteins are produced by the liver, immunoglobulins are produced by specialized leukocytes known as plasma cells. (Seek additional content for more information about immunoglobulins.) Globulins make up approximately 38 percent of the total plasma protein volume, in clinical levels of 1.0–1.5 g/dL blood.

• **Fibrinogen** is the third of the three major groups of plasma proteins. Like albumin and the alpha and beta globulins, fibrinogen is produced by the liver. It is essential for blood clotting. Fibrinogen accounts for about 7 percent of the total plasma protein volume, in clinical levels of 0.2–0.45 g/dL blood.

Other Plasma Solutes

In addition to proteins, plasma contains a wide variety of other substances. These include various electrolytes, such as sodium, potassium, and calcium ions; dissolved gases, such as oxygen, carbon dioxide, and nitrogen; various organic nutrients, such as vitamins, lipids, glucose, and amino acids; and metabolic wastes. All of these non-protein solutes combined contribute approximately 1 percent to the total volume of plasma.

Function

As plasma forms the liquid base of blood, the functions carried out by plasma and blood overlap. The multitude of functions include:

- *Coagulation*: fibrinogen plays a major role in blood clotting along with other procoagulants like thrombin and factor X.
- *Defense*: immunoglobulins and antibodies in plasma play an important role in the body's defense against bacteria, viruses, fungi, and parasites.
- *Maintenance of Osmotic Pressure*: the colloidal osmotic pressure is maintained at around 25 mmHg by the plasma proteins like albumin synthesized by the liver.

- *Nutrition*: transportation of nutrients like glucose, amino acids, lipids, and vitamins absorbed from the digestive tract to different parts of the body act as a source of fuel for growth and development.
- *Respiration*: transportation of respiratory gases, i.e., carrying oxygen to the various organs and carrying carbon dioxide back to the lungs for excretion.
- *Excretion*: the blood removes nitrogenous waste products produced after cellular metabolism and transports them to the kidney, lungs, and skin for excretion.
- *Hormones*: hormones are released into the blood and transported to their target organs.
- *Regulation of Acid-Base Balance*: plasma proteins contribute to acid-base balance through their buffering action.
- *Regulation of Body Temperature*: this is maintained by balancing heat loss and heat gain in the body.
- *Role in Erythrocyte Sedimentation Rate (ESR)*: fibrinogen, an acute phase reactant, increases during acute inflammatory conditions and contributes to the increase in ESR, which is used as a diagnostic and prognostic tool

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Clinical Considerations in Vascular Homeostasis

Any disorder that affects blood volume, vascular tone, or any other aspect of vascular functioning is likely to affect vascular homeostasis as well. That includes hypertension, hemorrhage, and shock.

Hypertension and Hypotension

New guidelines in 2017 from the American College of Cardiology and American Heart Association list normal blood pressure (BP) as less than 120/80 mm Hg and elevated BP as systolic P between 120–129 and diastolic P less than 80 mm Hg. Chronically elevated blood pressure is known clinically as **hypertension**. The new guidelines list hypertension that should be treated as 130/80 mm Hg. Tens of millions of Americans currently suffer from hypertension. Unfortunately, hypertension is typically a silent disorder; therefore, hypertensive patients may fail to recognize the seriousness of their condition and fail to follow their treatment plan. The result is often a heart attack or stroke. Hypertension may also lead to an aneurysm (ballooning of a blood vessel caused by a weakening of the wall), peripheral arterial disease (obstruction of vessels in peripheral regions of the body), chronic kidney disease, or heart failure.

Hemorrhage

Minor blood loss is managed by hemostasis and repair. Hemorrhage is a loss of blood that cannot be controlled by hemostatic mechanisms. Initially, the body responds to hemorrhage by initiating mechanisms aimed at increasing blood pressure and maintaining blood flow. Ultimately, however, blood volume will need to be restored, either through physiological processes or through medical intervention. In response to blood loss, stimuli from the baroreceptors trigger the cardiovascular centers to stimulate sympathetic responses to increase cardiac output and vasoconstriction. This typically prompts the heart rate to increase to about 180‑200 contractions per minute, restoring cardiac output to normal levels. Vasoconstriction of the arterioles increases vascular resistance, whereas constriction of the veins increases venous return to the heart. Both of these steps will help increase blood pressure. Sympathetic stimulation also triggers the release of epinephrine and norepinephrine, which enhance both cardiac

output and vasoconstriction. If blood loss were less than 20 percent of total blood volume, these responses together would usually return blood pressure to normal and redirect the remaining blood to the tissues.

Circulatory Shock

The loss of too much blood may lead to **circulatory shock**, a life-threatening condition in which the circulatory system is unable to maintain blood flow to adequately supply sufficient oxygen and other nutrients to the tissues to maintain cellular metabolism. It should not be confused with emotional or psychological shock. Typically, the patient in circulatory shock will demonstrate an increased heart rate but decreased blood pressure, but there are cases in which blood pressure will remain normal. Urine output will fall dramatically, and the patient may appear confused or lose consciousness. Urine output less than 1 mL/kg body weight/hour is cause for concern.

Unfortunately, shock is an example of a positive-feedback loop that, if uncorrected, may lead to the death of the patient. There are several recognized forms of shock:

· **Hypovolemic shock** in adults is typically caused by hemorrhage, although in children it may be caused by fluid losses related to severe vomiting or diarrhea. Other causes for hypovolemic shock include extensive burns, exposure to some toxins, and excessive urine loss related to diabetes insipidus or ketoacidosis. Typically, patients present with a rapid, almost tachycardic heart rate; a weak pulse often described as "thready;" cool, clammy skin, particularly in the extremities, due to restricted peripheral blood flow; rapid, shallow breathing; hypothermia; thirst; and dry mouth. Treatments generally involve providing intravenous fluids to restore the patient to normal function and various drugs such as dopamine, epinephrine, and norepinephrine to raise blood pressure.

· **Cardiogenic shock** results from the inability of the heart to maintain cardiac output. Most often, it results from a myocardial infarction (heart attack), but it may also be caused by arrhythmias, valve disorders, cardiomyopathies, cardiac failure, or simply insufficient flow of blood through the cardiac vessels. Treatment involves repairing the damage to the heart or its vessels to resolve the underlying cause, rather than treating cardiogenic shock directly.

· **Vascular shock** occurs when arterioles lose their normal muscular tone and dilate dramatically. It may arise from a variety of causes, and treatments almost always involve fluid replacement and medications, called inotropic or pressor agents, which restore tone to the muscles of the vessels. In addition, eliminating or at least alleviating the underlying cause of the condition is required. This might include antibiotics and antihistamines, or select steroids, which may aid in the repair of nerve damage. A common cause is **sepsis** (or septicemia), also called "blood poisoning," which is a widespread bacterial infection that results in an organismal-level inflammatory response known as **septic shock**. **Neurogenic shock** is a form of vascular shock that occurs with cranial or spinal injuries that damage the

cardiovascular centers in the medulla oblongata or the nervous fibers originating from this region. **Anaphylactic shock** is a severe allergic response that causes the widespread release of histamines, triggering vasodilation throughout the body.

· **Obstructive shock**, as the name would suggest, occurs when a significant portion of the vascular system is blocked. It is not always recognized as a distinct condition and may be grouped with cardiogenic shock, including pulmonary embolism and cardiac tamponade. Treatments depend upon the underlying cause and, in addition to administering fluids intravenously, often include the administration of anticoagulants, removal of fluid from the pericardial cavity, or air from the thoracic cavity, and surgery as required. The most common cause is a pulmonary embolism, a clot that lodges in the pulmonary vessels and interrupts blood flow. Other causes include stenosis of the aortic valve; cardiac tamponade, in which excess fluid in the pericardial cavity interferes with the ability of the heart to fully relax and fill with blood (resulting in decreased preload); and a pneumothorax, in which an excessive amount of air is present in the thoracic cavity, outside of the lungs, which interferes with venous return, pulmonary function, and delivery of oxygen to the tissues.

Anemia

When the total blood hemoglobin concentration falls below normal in anemia, each red blood cell produces increased amounts of 2,3-DPG. A normal hemoglobin concentration of 15 g per 100 ml unloads about 4.5 ml O2 per 100 ml at rest, as previously described. If the hemoglobin concentration were reduced by half, you might expect that the tissues would receive only half the normal amount of oxygen (2.25 ml O2 per 100 ml). However, an amount as great as 3.3 ml O2 per 100 ml is actually unloaded to the tissues under these conditions. This occurs as a result of a rise in 2,3-DPG production that causes a decrease in the affinity of hemoglobin for oxygen.

Anemia is a decrease in the ability of the blood to carry oxygen due to (1) a decrease in the total number of erythrocytes, each having a normal quantity of hemoglobin; (2) a diminished concentration of hemoglobin per erythrocyte; or (3) a combination of both. Anemia has a wide variety of causes, some of which are listed bellow:

1. Dietary deficiencies of iron (***iron-deficiency anemia***), vitamin B12, or folic acid
2. Bone marrow failure due to toxic drugs or cancer
3. Blood loss from the body (hemorrhage)
4. Inadequate secretion of erythropoietin in kidney disease
5. Excessive destruction of erythrocytes (for example, sickle-cell disease)

Inherited Defects in Hemoglobin Structure and Function

A number of hemoglobin diseases are produced by congenital (inherited) defects in the protein part of hemoglobin. **Sickle-cell anemia,** (also called sickle-cell anemia) a disease that occurs almost exclusively in people of African heritage, is carried in a recessive state by 8% to 11% of the African American population, making it the most common monogenic (single gene) disorder. This disease occurs when a person inherits the affected gene from each parent and produces hemoglobin S instead of normal hemoglobin A. Hemoglobin S differs from hemoglobin A in that one amino acid is substituted for another (a valine for a glutamic acid) in the beta chains of hemoglobin, due to a single base change in the DNA of the gene for the beta chains.

Under conditions of low PO2 , when the hemoglobin is deoxygenated, hemoglobin S polymerizes into long fibers. This causes the red blood cells to have their characteristic sickle shape (fig. 3.1). It also reduces their flexibility, which hinders their ability to pass through narrow vessels and thereby reduces blood flow through organs, causing severe pain and organ damage. In addition, the long fibers of hemoglobin S damage the plasma membrane of red blood cells and thereby promote hemolysis and hemolytic anemia. These effects reduce a patient's life expectancy.

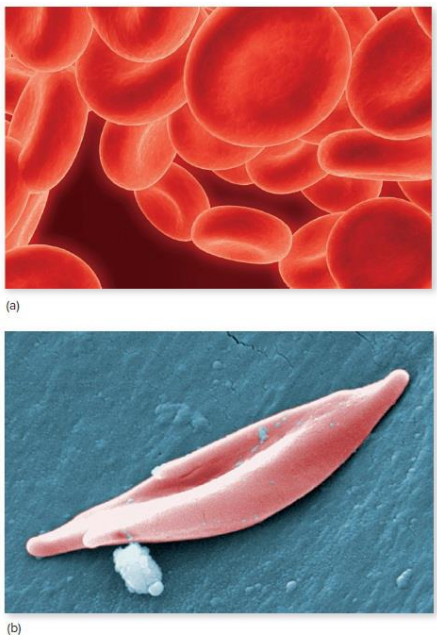

FIGURE 3.1 Sickle-cell anemia. (a) Normal red blood cells. (b) Sickled red blood cell as seen in the scanning electron microscope.

Sickle-cell disease is an example of a disease that is manifested fully only in people homozygous for the mutated gene (that is, they have two copies of the mutated gene, one from each parent). In heterozygotes (one mutated copy and one normal gene), people who are said to have sickle cell trait, the normal gene codes for normal hemoglobin and the mutated gene for the abnormal hemoglobin. The erythrocytes in this case contain both types of hemoglobin, but symptoms are observed only when the oxygen level is unusually low, as at high altitude. The persistence of the sickle-cell mutation in humans over generations

is due to the fact that heterozygotes are more resistant to malaria, a blood infection caused by a protozoan parasite that is spread by mosquitoes in tropical regions.

Thalassemia is a family of diseases affecting the protein portion of hemoglobin. These diseases involve impaired synthesis of either the alpha chain (alpha thalassemia) or the beta chain (beta thalassemia) of the hemoglobin protein, and are among the most common of the monogenic (single-gene) diseases. Alpha thalassemia is the more prevalent, occurring at high frequency across the equatorial regions, but beta thalassemia is the more clinically serious form that requires regular blood transfusions. There are over 100 different genetic forms of alpha thalassemia, and over 200 different point mutations in DNA that can produce beta thalassemia. The diversity of mutations produces a wide range of clinical symptoms.

CATABOLISM OF HEMOGLOBIN

When old red blood cells are destroyed by tissue macrophages, the globin portion of the hemoglobin molecule is split off, and the heme is converted to **biliverdin.** The enzyme involved is a subtype of heme oxygenase, and CO is formed in the process. CO is an intercellular messenger. In humans, most of the biliverdin is converted to **bilirubin** and excreted in the bile. The iron from the heme is reused for hemoglobin synthesis. Exposure of the skin to white light converts bilirubin to lumirubin, which has a shorter half-life than bilirubin. **Phototherapy** (exposure to light) is of value in treating infants with jaundice due to hemolysis. Iron is essential for hemoglobin synthesis; if blood is lost from the body and the iron deficiency is not corrected, **iron deficiency anemia** results.

Iron-Deficiency Anemia

Iron-deficiency anemia (IDA) is one of the more common causes of anemia. It typically results from insufficient iron intake, poor gastrointestinal absorption, or overt or occult blood loss. Distinguishing iron deficiency from other causes of anemia is crucial for initiating appropriate treatment, as is identifying the underlying cause of iron deficiency. The focus will be on IDA in adults..

Definitions and Diagnosis

Iron deficiency is a state in which reduction of iron stores precedes development of overt iron-deficiency anemia. It may persist without progression. Iron-deficiency anemia is a more severe condition in which low levels of iron are associated with anemia and the presence of microcytic hypochromic red cells in the circulation, the relative number of which reflects the severity of the iron deficiency. Iron-restricted erythropoiesis refers to a state in which delivery of iron to erythroid precursors for Hb synthesis is impaired, no matter how replete the stores.

Iron stores may be normal or increased because iron is sequestered within macrophages as in the anemia of chronic disease (ACD). The latte, it is seen in patients with autoimmune disorders, cancer, infections, and chronic kidney diseases.

Separation of IDA from ACD is often difficult since both can co-exist, particularly in the elderly and in patients with chronic kidney disease However, a substantial fraction of the anemia commonly found in the elderly patient occurs in the absence of iron deficiency or elevated hepcidin levels.

Functional iron deficiency is a state of iron-poor erythropoiesis in which there is insufficient mobilization of iron from stores in the presence of increased demands. This is typically observed following treatment with erythropoiesis-stimulating agents (ESAs).

Vitamin B12 or folate deficiency anemia

Objectives:

- Explain the pathophysiology of vitamin B12 deficiency.
- Review the risk factors for developing a vitamin B12 deficiency.
- Describe the typical presentation of a patient with vitamin B12 deficiency.
- Explain the importance of improving care coordination amongst the interprofessional team to enhance the delivery of care for patients with vitamin B12 deficiency.
- Access free multiple choice questions on this topic.

Vitamin B12, also known as cobalamin, is a water-soluble vitamin that is derived from animal products such as red meat, dairy, and eggs. Intrinsic factor is a glycoprotein produced by parietal cells in the stomach and necessary for the absorption of vitamin B12 in the terminal ileum. Once absorbed, vitamin B12 is used as a cofactor for enzymes that are involved in the synthesis of deoxyribonucleic acid (DNA), fatty acids, and myelin. Vitamin B12 deficiency can lead to hematologic and neurological symptoms. Vitamin B12 is stored in excess in the liver, decreasing the likelihood of deficiency. However, in cases in which vitamin B12 cannot be absorbed, for example, due to dietary insufficiency, malabsorption, or lack of intrinsic factor, hepatic stores are depleted, and deficiency ensues.

Vitamin B12 deficiency has 3 primary etiologies:

- Autoimmune: Pernicious anemia is an autoimmune condition in which antibodies to intrinsic factor are produced. Anti-intrinsic factor antibodies bind to and inhibit the effects of intrinsic factor, resulting in an inability of B12 to be absorbed by the terminal ileum.
- Malabsorption: Parietal cells in the stomach produce intrinsic factor; therefore, any patient with a history of gastric bypass surgery may be at risk for developing a B12 deficiency because their new alimentary pathway bypasses the site of intrinsic factor production. In patients with normal intrinsic factor production, any damage to the terminal ileum, such as surgical resection due to Crohn's disease, will impair the absorption of B12 and lead to a deficiency. Other damage to the small intestine, such

as inflammation from celiac disease or infection with the tapeworm Diphyllobothrium latum, may also result in a B12 deficiency.

- Dietary Insufficiency: Vitamin B12 is stored in excess in the liver; however, patients who have followed a strict vegan diet for approximately three years may develop a B12 deficiency from a lack of dietary intake.

What causes vitamin B12 deficiency anemia?

Vitamin B12 deficiency anemia is more common in people whose families come from northern Europe. It is caused by one of the following:

- Lack of intrinsic factor. Intrinsic factor is a protein made in the stomach. It is needed to absorb vitamin B12. This type of B12 deficiency anemia is called pernicious anemia.
- Surgery that removes or bypasses the end of the small intestine. This part of the small intestine is where vitamin B12 is absorbed.

The inability to make intrinsic factor may be caused by several things, such as:

- Chronic gastritis
- Surgery to remove all or part of the stomach (gastrectomy)
- An autoimmune condition, where the body attacks its own tissues

Other types of megaloblastic anemia may be linked with type 1 diabetes, thyroid disease, and a family history of the disease.

Jaundice

Because the duct from the pancreas joins the common bile duct just before it enters the duodenum, a gallstone that becomes lodged at this point prevents or limits both bile and pancreatic secretions from entering the intestine. This results in failure to both neutralize acid and adequately digest most organic nutrients, not just fat. The end results are severe nutritional deficiencies. The buildup of very high pressure in a blocked common bile duct is transmitted back to the liver and interferes with the further secretion of bile. As a result, bilirubin, which is normally secreted into the bile by uptake from the blood in the liver, accumulates in the blood and diffuses into tissues, producing a yellowish coloration of the skin and eyes known as jaundice.

As explained earlier, all transfusion reactions eventually cause immediate hemolysis resulting from hemolysins or later hemolysis resulting from phagocytosis of agglutinated cells. Hemoglobin released from the RBCs is then converted by the phagocytes into bilirubin and later excreted in the bile by the liver. The concentration of bilirubin in the body fluids often rises high enough to cause jaundice—that is, the person's internal tissues and skin become colored with yellow bile pigment. However, if liver function is normal, the bile pigment will be excreted into the intestines by way of the liver bile, so

jaundice usually does not appear in an adult unless more than 400 milliliters of blood are hemolyzed in less than a day.

Effect of Mother's Antibodies on the Fetus. After anti-Rh antibodies have formed in the mother, they diffuse slowly through the placental membrane into the fetus's blood. There they cause agglutination of the fetus's blood. The agglutinated RBCs subsequently hemolysis, releasing hemoglobin into the blood. The fetus's macrophages then convert the hemoglobin into bilirubin, which causes the baby's skin to become yellow (jaundiced). The antibodies can also attack and damage other cells of the body.

Clinical Picture of Erythroblastosis.

The jaundiced, erythroblastotic newborn baby is usually anemic at birth, and the anti-Rh agglutinins from the mother usually circulate in the infant's blood for another 1 to 2 months after birth, destroying more and more RBCs. The hematopoietic tissues of the infant attempt to replace the hemolyzed RBCs. The liver and spleen become greatly enlarged and produce RBCs in the same manner that they normally do during the middle of gestation. Because of the rapid production of RBCs, many early forms of RBCs, including many nucleated blastic forms, are passed from the baby's bone marrow into the circulatory system, and it is because of the presence of these nucleated blastic RBCs that the disease is called erythroblastosis fetalis. Although the severe anemia of erythroblastosis fetalis is usually the cause of death, many children who barely survive the anemia exhibit permanent mental impairment or damage to motor areas of the brain because of precipitation of bilirubin in the neuronal cells, causing the destruction of many of these cells, a condition called kernicterus.

PHYSIOLOGY

Assist. Prof. Dr. Fatimah A Jasim

Reference: Human Physiology 15th ed. By Stuart Fox

VANDER' S Human Physiology 15th ed. By ERIC P. WIDMAIER

Anatomy and Physiology, 2nd ed , By Robin J. Heyden

Functions and components of the circulatory system

A unicellular organism can provide for its own maintenance and continuity by performing the wide variety of functions needed for life. By contrast, the complex human body is composed of specialized cells that depend on one another. Because most are firmly implanted in tissues, their oxygen and nutrients must be brought to them, and their waste products removed. Therefore, a highly effective means of transporting materials within the body is needed.

The blood serves this transportation function. An estimated 60,000 miles of vessels throughout the body of an adult ensure that continued sustenance reaches each of the trillions of living cells. However, the blood can also transport disease causing viruses, bacteria, and their toxins. To guard against this, the circulatory system has protective mechanisms—the white blood cells and the lymphatic system. In order to perform its various functions, the circulatory system works together with the respiratory, urinary, digestive, endocrine, and integumentary systems in maintaining homeostasis.

Major Components of the Circulatory System

The **circulatory system** consists of two subdivisions: the cardiovascular system and the lymphatic system. The **cardiovascular system** consists of the heart andblood vessels, and the **lymphatic system,** which includes lymphatic vessels and lymphoid tissues within the spleen, thymus, tonsils, and lymph nodes.

Cardiovascular system

The **heart** is a four-chambered double pump. Its pumping action creates the pressure head needed to push blood through the *pulmonary circulation* (to the lungs) and through the *systemic circulation* (to the rest of the body). At rest, the heart of an adult pumps about 5 liters of blood per minute through each

circulation. At this rate, it takes about 1 minute for blood to be circulated to the most distal extremity and back to the heart.

Blood vessels form a tubular network that permits blood to flow from the heart to all the living cells of the body and then back to the heart. *Arteries* carry blood away from the heart, whereas *veins* return blood to the heart. Arteries and veins are continuous with each other through smaller blood vessels.

Arteries branch extensively to form a "tree" of progressively smaller vessels. The smallest of the arteries are called *arterioles.* Blood passes from the arterial to the venoussystem in microscopic *capillaries,* which are the thinnest and most numerous of the blood vessels. All exchanges of fluid, nutrients, and wastes between the blood and tissues occur across the walls of capillaries. Blood flows through capillaries into microscopic veins called *venules,* which deliver blood into progressively larger veins that eventually return the blood to the heart.

Blood Typing

LEARNING OBJECTIVES

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

- Compare and contrast ABO and Rh blood groups
- Identify which blood groups may be safely transfused into patients with different ABO types
- Discuss the pathophysiology of hemolytic disease of the newborn

The ABO Blood Group

Although the **ABO blood group** name consists of three letters, ABO blood typing designates the presence or absence of just two antigens, A and B. Both are glycoproteins. People whose erythrocytes have A antigens on their erythrocyte membrane surfaces are designated blood type A, and those whose erythrocytes have B antigens are blood type B. People can also have both A and B antigens on their erythrocytes, in which case they are blood type AB. People with neither A nor B antigens are designated blood type O. ABO blood types are genetically determined.

The body must be exposed to a foreign antigen before an antibody can be produced. ABO blood group antigens are found in foods and microbes throughout nature. Thus, the human immune system is exposed to A and B antigens at an early age and antibodies are formed naturally. Individuals with type A blood—without any prior exposure to incompatible blood—have naturally-formed antibodies to the B antigen circulating in their blood plasma. These antibodies, referred to as anti-B antibodies, will cause agglutination and hemolysis if they ever encounter erythrocytes with B antigens. Similarly, an individual with type B blood has naturally-formed anti-A antibodies.

Individuals with type AB blood, which has both antigens, do not have naturally-formed antibodies to either of these. People with type O blood lack antigens A and B on their erythrocytes, but both anti-A and anti-B antibodies circulate in their blood plasma.

Rh Blood Groups

The **Rh blood group** is classified according to the presence or absence of a second erythrocyte antigen identified as Rh. (It was first discovered in a type of primate known as a rhesus macaque, which is often used in research, because its blood is similar to that of humans.) Although dozens of Rh antigens have been identified, only one, designated D, is clinically important. Those who have the Rh D antigen present on their erythrocytes—about 85 percent of Americans—are described as Rh positive (Rh+) and those who lack it are Rh negative (Rh–). Note that the Rh group is distinct from the ABO group, so any individual, no matter their ABO blood type, may have or lack this Rh antigen. When identifying a patient's blood type, the Rh group is designated by adding the word positive or negative to the ABO type. For example, A positive (A+) means ABO group A blood with the Rh antigen present, and AB negative (AB–) means ABO group AB blood without the Rh antigen.

In contrast to the ABO group antibodies, which are preformed, antibodies to the Rh antigen are produced only in Rh− individuals after exposure to the antigen. This process, called sensitization, occurs following a transfusion with Rh incompatible blood or, more commonly, with the birth of an Rh+ baby to an Rh− person. Problems are rare in a first pregnancy, since the baby's Rh+ cells rarely cross the placenta (the organ of gas and nutrient exchange between the fetus and the pregnant person). However, during or immediately after birth, the Rh− parent can be exposed to the baby's Rh+ cells (Figure 1). Research has shown that this occurs in about 13−14 percent of such pregnancies. After exposure, the immune system of the person who has given birth begins to generate anti-Rh antibodies. If the same person should then become pregnant with another Rh+ baby, the Rh antibodies they have produced can cross the placenta into the fetal bloodstream and destroy the fetal RBCs. This condition, known as **hemolytic disease of the newborn (HDN)** or **erythroblastosis fetalis**, may cause anemia in mild cases, but the agglutination and hemolysis can be so severe that without treatment the fetus may die in the womb or shortly after birth.

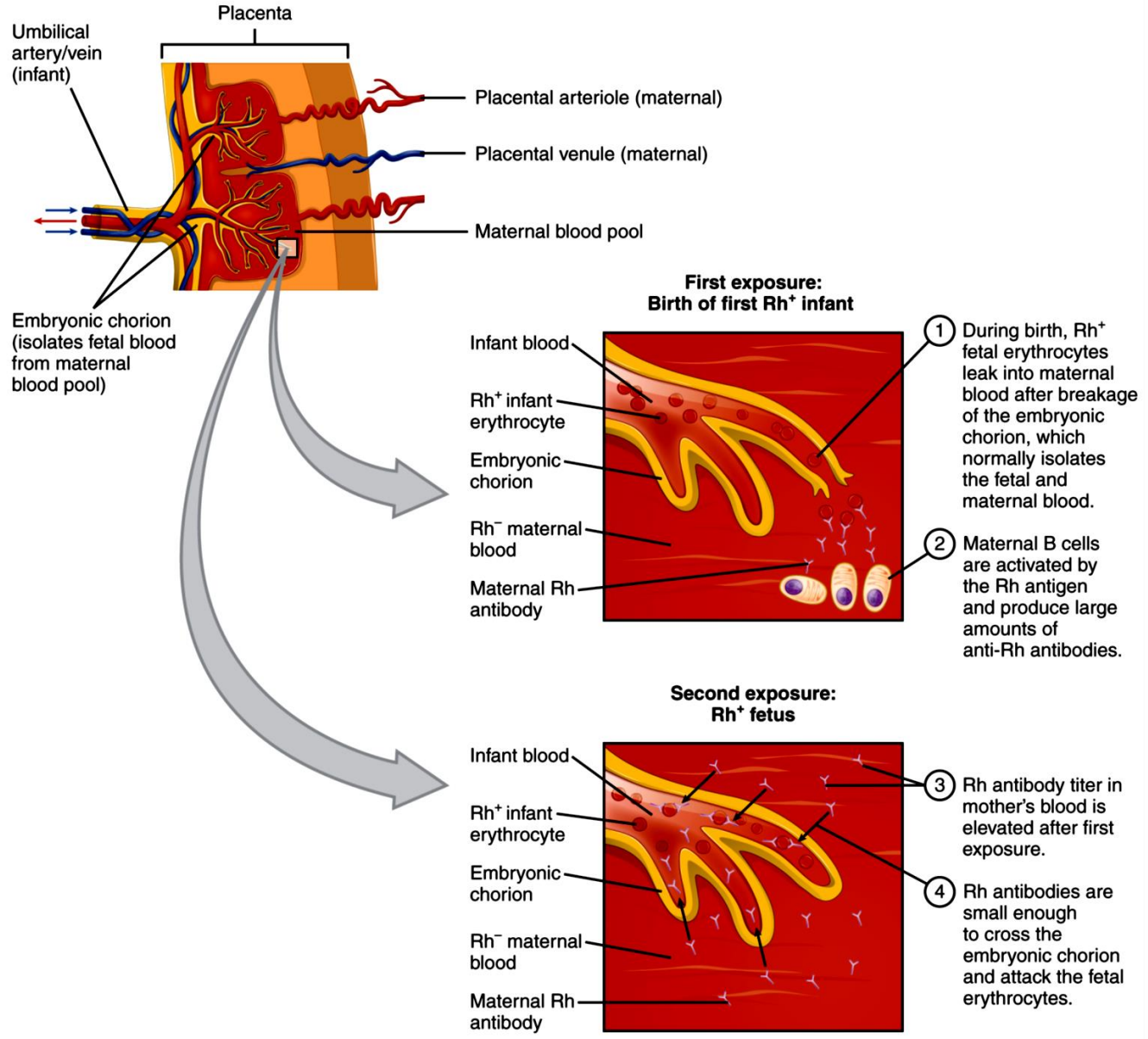

FIGURE 18.15 Erythroblastosis Fetalis The first exposure of an Rh− person to Rh+ erythrocytes during pregnancy induces sensitization. Anti-Rh antibodies begin to circulate in the pregnant person's bloodstream. A second exposure occurs with a subsequent pregnancy with an Rh+ fetus in the uterus. During that subsequent pregnancy, the pregnant person's anti-Rh antibodies may cross the placenta and enter the fetal bloodstream, causing agglutination and hemolysis of fetal erythrocytes.

A drug known as RhoGAM, short for Rh immune globulin, can temporarily prevent the development of Rh antibodies in the Rh− parent, thereby averting this potentially serious disease for the fetus. RhoGAM antibodies destroy any fetal Rh+ erythrocytes that may cross the placental barrier. RhoGAM is normally administered to Rh− pregnant people during weeks 26−28 of pregnancy and within 72 hours following birth. It has proven remarkably effective in decreasing the incidence of HDN. Earlier we noted that the incidence of HDN in an Rh+ subsequent pregnancy to an Rh− person is about 13‑14 percent without preventive treatment.

PHYSIOLOGY

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STRUCTURE OF THE HEART

LEARNING OUTCOMES

After studying this section, you should be able to:

Distinguish between the systemic and the pulmonary circulation.

Describe the structure of the heart and its components.

About the size of a fist, the hollow, cone-shaped **heart** is divided into four chambers. The right and left **atria** (singular, *atrium*) receive blood from the venous system; the right and left **ventricles** pump blood into the arterial system. The right atrium and ventricle (sometimes called the *right pump*) are separated from the left atrium and ventricle (the *left pump*) by a muscular wall, or *septum.* This septum normally prevents mixture of the blood from the two sides of the heart.

Between the atria and ventricles, there is a layer of dense connective tissue known as the **fibrous skeleton** of the heart. Bundles of myocardial cells in the atria attach to the upper margin of this fibrous skeleton and form a single functioning unit, or *myocardium.*

The myocardial cell bundles of the ventricles attach to the lower margin and form a different myocardium. As a result, the myocardia of the atria and ventricles are structurally and functionally separated from each other, and special conducting tissue is needed to carry action potentials from the atria to the ventricles. The connective tissue of the fibrous skeleton also forms rings, called *annuli fibrosi*, around the four heart valves, providing a foundation for the support of the valve flaps.

Cardiac Muscle and Electrical Activity

LEARNING OBJECTIVES

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

- Describe the structure of cardiac muscle
- Identify and describe the components of the conducting system that distributes electrical impulses through the heart
- Compare the effect of ion movement on membrane potential of cardiac conductive and contractile cells
- Relate characteristics of an electrocardiogram to events in the cardiac cycle
- Identify blocks that can interrupt the cardiac cycle

Cardiac Muscle

There are two major types of cardiac muscle cells: myocardial contractile cells and myocardial conducting cells. The **myocardial contractile cells** constitute the bulk (99 percent) of the cells in the atria and ventricles. Contractile cells conduct impulses and are responsible for contractions that pump blood through the body. The **myocardial conducting cells** (1 percent of the cells) form the conduction system of the heart. Except for Purkinje cells, they are generally much smaller than the contractile cells and have few of the myofibrils or filaments needed for contraction. Their function is similar in many respects to neurons, although they are specialized muscle cells. Myocardial conduction cells initiate and propagate the action potential (the electrical impulse) that travels throughout the heart and triggers the contractions that propel the blood.

Structure of Cardiac Muscle

Compared to the giant cylinders of skeletal muscle, cardiac muscle cells, or cardiomyocytes, are considerably shorter with much smaller diameters. Cardiac muscle also demonstrates striations, the alternating pattern of dark A bands and light I bands attributed to the precise arrangement of the myofilaments and fibrils that are organized in sarcomeres along the length of the cell (Figure 1 **a**).

These contractile elements are virtually identical to skeletal muscle. T (transverse) tubules penetrate from the surface plasma membrane, the sarcolemma, to the interior of the cell, allowing the electrical impulse to reach the interior. The T tubules are only found at the Z discs, whereas in skeletal muscle, they are found at the junction of the A and I bands. Therefore, there are one-half as many T tubules in cardiac muscle as in skeletal muscle.

In addition, the sarcoplasmic reticulum stores few calcium ions, so most of the calcium ions must come from outside the cells. The result is a slower onset of contraction. Mitochondria are plentiful, providing energy for the contractions of the heart. Typically, cardiomyocytes have a single, central nucleus, but two or more nuclei may be found in some cells. Cardiac muscle cells branch freely. A junction between two adjoining cells is marked by a critical structure called an **intercalated disc**, which helps support the synchronized contraction of the muscle (Figure 1 **b**).

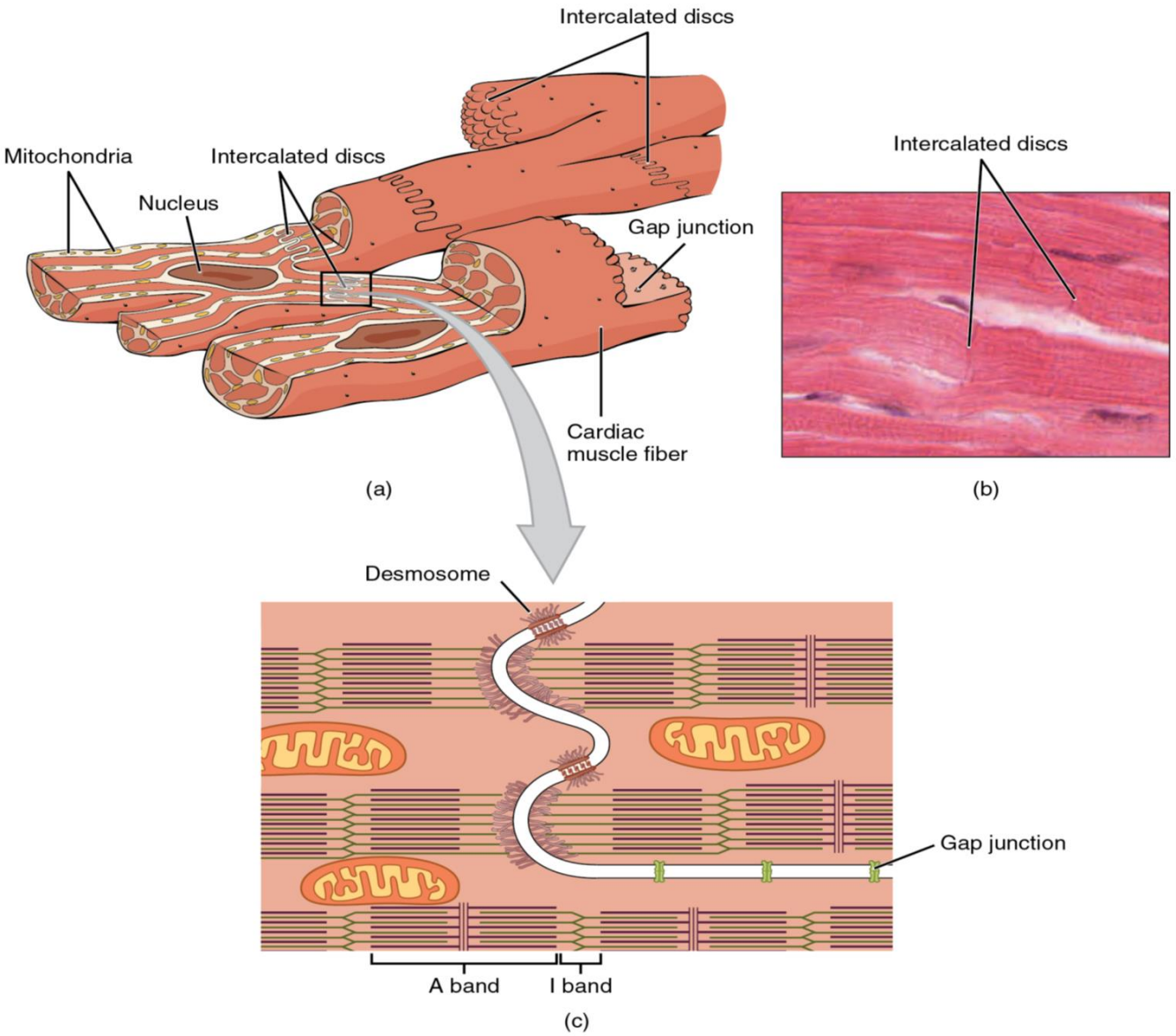

FIGURE 1 Cardiac Muscle (a) Cardiac muscle cells have myofibrils composed of myofilaments arranged in sarcomeres, T tubules to transmit the impulse from the sarcolemma to the interior of the cell, numerous mitochondria for energy, and intercalated discs that are found at the junction of different cardiac muscle cells. (b) A photomicrograph of cardiac muscle cells shows the nuclei and intercalated discs. (c) An intercalated disc connects cardiac muscle cells and consists of desmosomes and gap junctions.

The sarcolemmas from adjacent cells bind together at the intercalated discs. They consist of desmosomes, specialized linking proteoglycans, tight junctions, and large numbers of gap junctions that allow the passage of ions between the cells and help to synchronize the contraction (Figure 1 **c**).

Intercellular connective tissue also helps to bind the cells together. The importance of strongly binding these cells together is necessitated by the forces exerted by contraction.

CARDIAC CYCLE

The two atria fill with blood and then contract simultaneously. This is followed by simultaneous contraction of both ventricles, which sends blood through the pulmonary and systemic circulations. Pressure changes in the atria and ventricles as they go through the cardiac cycle are responsible for the flow of blood through the heart chambers and out into the arteries.

LEARNING OUTCOMES

After studying this section, you should be able to:

Describe the cardiac cycle in terms of systole and diastole of the atria and ventricles.

Explain how the pressure differences within the heart chambers are responsible for blood flow during the cardiac cycle.

The **cardiac cycle** is the repeating pattern of contraction and relaxation of the heart. The phase of contraction is called **systole,** and the phase of relaxation is called **diastole.** When these terms are used without reference to specific chambers, they refer to contraction and relaxation of the ventricles. It should be noted, however, that the atria also contract and relax. There is an atrial systole and diastole. Atrial contraction occurs toward the end of diastole, when the ventricles are relaxed; when the ventricles contract during systole, the atria are relaxed (**fig. 2**).

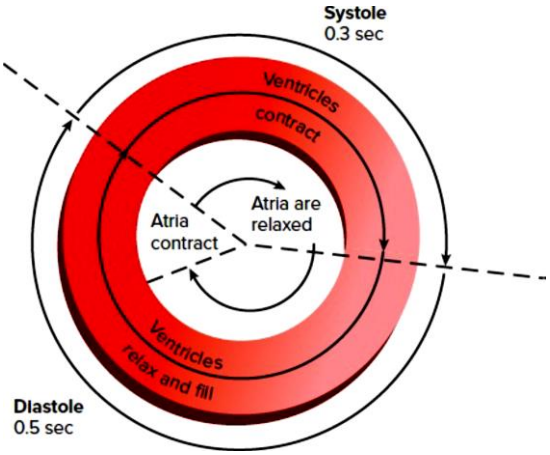

FIGURE 2 The cardiac cycle of ventricular systole and diastole. Contraction of the atria occurs in the last 0.1 second of ventricular diastole. Relaxation of the atria occurs during ventricular systole. The durations given for systole and diastole relate to a cardiac rate of 75 beats per minute.

The heart has a two-step pumping action. The right and left atria contract almost simultaneously, followed by contraction of the right and left ventricles 0.1 to 0.2 second later. During the time when both the atria and ventricles are relaxed, the venous return (blood from the veins) fills the atria. The buildup of pressure from the atrial filling causes the AV valves to open and blood to flow from the atria to the ventricles. The ventricles are about 80% filled with blood even before the atria contract. Contraction of the atria adds the final 20% to the **end-diastolic volume**, which is the total volume of blood in the ventricles at the end of diastole.

Contraction of the ventricles in systole ejects about two-thirds (the *ejection fraction*) of the blood they contain—the amount ejected is the **stroke volume**—leaving one-third of the initial amount left in the ventricles as the *end-systolic volume.* The ventricles then fill with blood during the next cycle. At an average **cardiac rate** of 75 beats per minute, each cycle lasts 0.8 second; 0.5 second is spent in diastole, and systole takes 0.3 second (fig. 2).

THE PULSE

The ventricles regularly pump blood into the arteries about 70 to 80 times a minute. The force of ventricular contraction starts a wave of increased pressure that begins at the heart and travels along the arteries. This wave, called the **pulse**, can be felt in any artery that is relatively close to the surface, particularly if the vessel can be pressed down against a bone. At the wrist, the radial artery passes over the bone on the forearm's thumb side, and

the pulse is most commonly obtained here. Other vessels sometimes used for taking the pulse are the carotid artery in the neck and the dorsalis pedis on the top of the foot.

Normally, the pulse rate is the same as the heart rate, but if a heartbeat is abnormally weak, or if the artery is obstructed, the beat may not be detected as a pulse. In checking another person's pulse, it is important to use your second or third finger. If you use your thumb, you may be feeling your own pulse. When taking a pulse, it is important to gauge its strength as well as its regularity and rate.

Various factors may influence the pulse rate. We describe just a few here:

■ The pulse is somewhat faster in small people than in large people, and usually is slightly faster in women than in men.

■ In a newborn infant, the rate may be from 120 to 140 beats/ min. As the child grows, the rate tends to become slower.

■ Muscular activity influences the pulse rate. During sleep, the pulse may slow down to 60 beats/min, whereas during strenuous exercise, the rate may go up to well over 100 beats/min. For a person in good condition, the pulse does not go up as rapidly as it does in an inactive person, and it returns to a resting rate more quickly after exercise.

■ Emotional disturbances may increase the pulse rate.

■ Pulse rate increases with increased temperature, as in cases of infection.

■ Excessive secretion of thyroid hormone may cause a rapid pulse.

Pulmonary and Systemic Circulations

Blood whose oxygen content has become partially depleted and whose carbon dioxide content has increased as a result of tissue metabolism returns to the right atrium. This blood then enters the right ventricle, which pumps it into the ***pulmonary trunk*** and ***pulmonary arteries***. The pulmonary arteries branch to transport blood to the lungs, where gas exchange occurs between the lung capillaries and the air sacs (alveoli) of the lungs. Oxygen diffuses from the air to the capillary blood, whereas carbon dioxide diffuses in the opposite direction.

The blood that returns to the left atrium by way of the *pulmonary veins* is therefore enriched in oxygen and partially depleted of carbon dioxide. Thus, unlike all of the other arteries and veins in the body, the pulmonary arteries carry blood that is lower in oxygen, whereas the pulmonary veins carry oxygen-rich blood. The path of blood from the heart (right ventricle), through the lungs, and back to the heart (left atrium) completes one circuit: the **pulmonary circulation.**

Oxygen-rich blood in the left atrium enters the left ventricle and is pumped into a very large, elastic artery−the *aorta*. The aorta ascends for a short distance, makes a U-turn, and then descends through the thoracic (chest) and abdominal cavities. Arterial branches from the aorta supply oxygen-rich blood to all of the organ systems and are thus part of the **systemic circulation.** As a result of cellular respiration, the oxygen concentration is lower and the carbon dioxide concentration is higher in the tissues than in the capillary blood. Blood that drains from the tissues into the systemic veins is thus partially depleted of oxygen and increased in carbon dioxide content. These veins ultimately empty into two large veins−the *superior* and *inferior venae cavae*− that return the oxygen-poor blood to the right atrium. This completes the systemic circulation: from the heart (left ventricle), through the organ systems, and back to the heart (right atrium). The systemic and pulmonary circulations are illustrated in **figure 3**, and their characteristics are summarized in table 1.

The numerous small muscular arteries and arterioles of the systemic circulation present greater resistance to blood flow than that in the pulmonary circulation. Despite the differences in resistance, the rate of blood flow through the systemic circulation must be matched to the flow rate of the pulmonary circulation. Because the amount of work performed by the left ventricle is greater (by a factor of 5 to 7) than that performed by the right ventricle, it is not surprising that the muscular wall of the left ventricle is thicker (8 to 10 mm) than that of the right ventricle (2 to 3 mm) so that it can contract more strongly to match its output to that of the right ventricle.

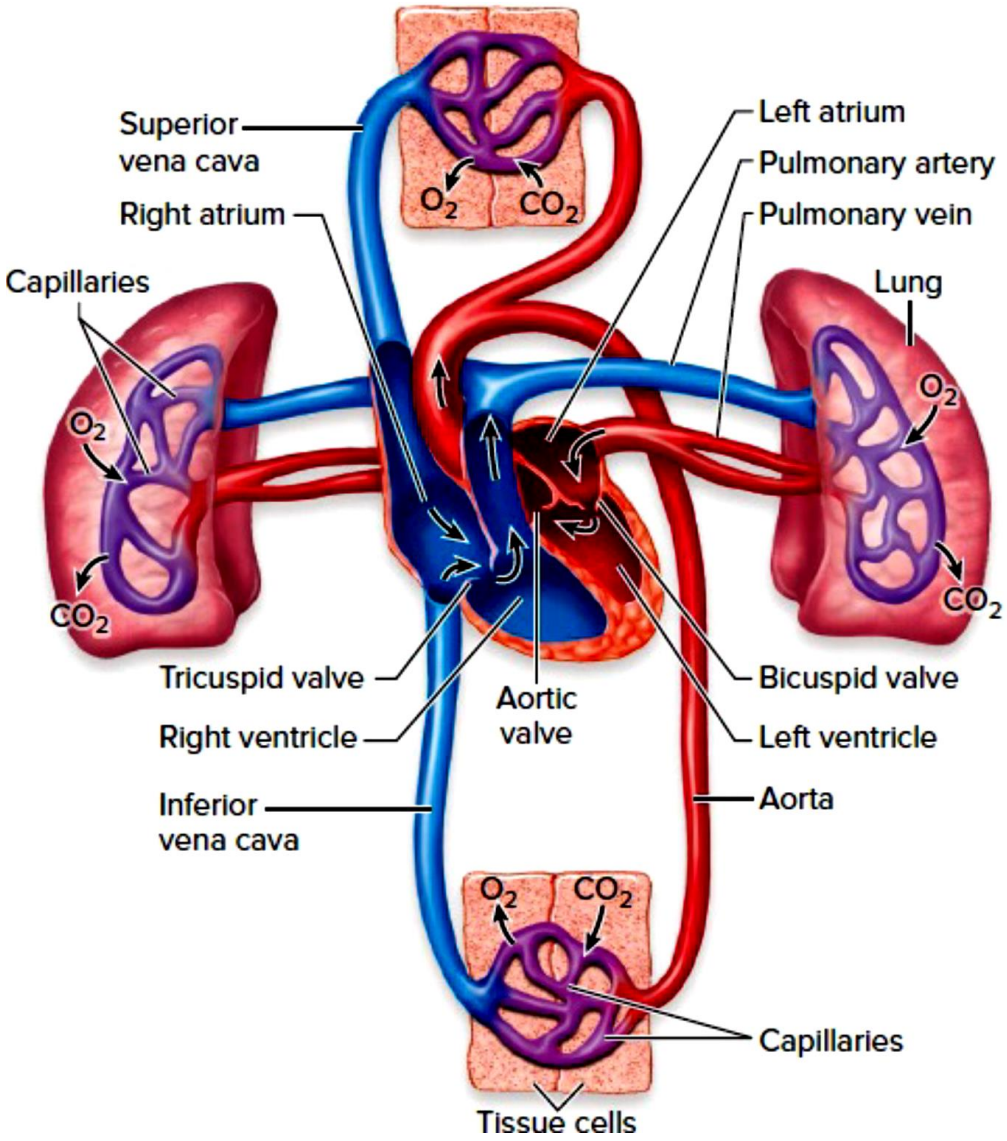

FIGURE 3 A diagram of the circulatory system. The systemic circulation includes the aorta and venae cava; the pulmonary circulation includes the pulmonary arteries and pulmonary veins.

TABLE 7.1 | Summary of the Pulmonary and Systemic Circulations

	Source	Arteries	O2 Content of Arteries	O2 Content of Veins	Veins	Termination
Pulmonary Circulation	Right ventricle	Pulmonary arteries	Low	Pulmonary veins	High	Left atrium
Systemic Circulation	Left ventricle	Aorta and its branches	High	Superior and inferior venae cava and their branches*	Low	Right atrium
*Blood from the coronary circulation does not enter the venae cava, but instead returns direct into the right atrium via the coronary sinus.						

Pressure Changes During the Cardiac Cycle

When the heart is in diastole, the pressure in the systemic arteries averages about 80 mmHg (millimeters of mercury). These events in the cardiac cycle then occur (fig. 4):

1. As the ventricles begin their contraction, the intraventricular pressure (pressure inside the ventricles) rises, causing the AV valves to snap shut and produce the first heart sound. At this time, the ventricles are neither being filled with blood (because the AV valves are closed) nor ejecting blood (because the intraventricular pressure has not yet risen sufficiently to open the semilunar valves). This is the phase of *isovolumetric contraction.*
2. When the pressure in the left ventricle becomes greater than the pressure in the aorta, the phase of *ejection* begins as the semilunar valves open. The pressure in the left ventricle and aorta rises to about 120 mmHg (fig. 4) when ejection begins and the ventricular volume decreases.
3. As the pressure in the ventricles falls below the pressure in the arteries, the back pressure causes the semilunar valves to snap shut and produce the second heart sound. The pressure in the aorta falls to 80 mmHg, while pressure in the left ventricle falls to 0 mmHg. During *isovolumetric relaxation*, both the AV and semilunar valves are closed. This phase lasts until the pressure in the ventricles falls below the pressure in the atria.
4. When the pressure in the ventricles falls below the pressure in the atria, the AV valves open and a phase of *rapid filling* of the ventricles occurs.
5. *Atrial contraction* (*atrial systole*) delivers the final amount of blood into the ventricles immediately prior to the next phase of isovolumetric contraction of the ventricles.

Similar events occur in the right ventricle and pulmonary circulation, but the pressures are lower. The maximum pressure produced at systole in the right ventricle is 25 mmHg, which falls to a low of 8 mmHg at diastole. The arterial pressure rises as a result of ventricular systole (due to blood ejected into the arterial system) and falls during ventricular diastole (fig. 4). Because of this, a person's

cardiac cycle can be followed by measuring the systolic and diastolic blood pressures, and by palpating (feeling) the pulse. A pulse is felt (for example, in the radial artery of the wrist) when the arterial pressure rises from diastolic to systolic levels and pushes against the examiner's finger.

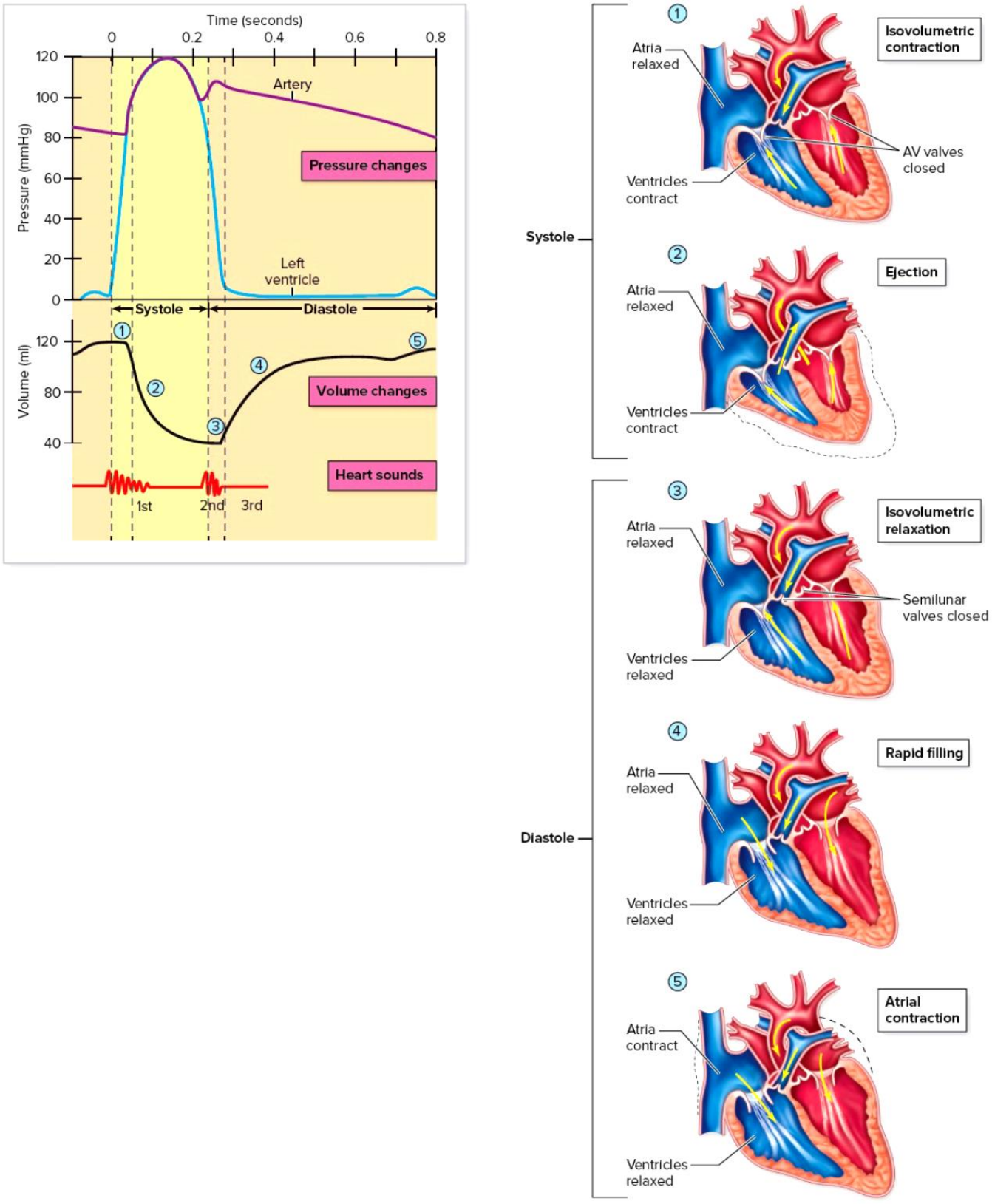

FIGURE 4 Pressure changes in the left ventricle and their effects during the cardiac cycle. The figure shows the effects of left ventricular pressure changes on left ventricular volume and arterial pressure and the correlation of these with the heart sounds. The numbers refer to the events described in the text and illustrated in the portion of the figure on the right.

Figure 4 reveals an inflection in the descending portion of the arterial pressure graph, which cannot be felt on palpation. This inflection is called the *dicrotic notch* and is produced by closing of the aortic and pulmonic semilunar valves. Closing of these valves produces the second heart sound and the dicrotic notch during the phase of isovolumetric relaxation at the beginning of diastole.

An electrocardiogram (ECG) also allows an examiner to follow the cardiac cycle of systole and diastole (see fig. 4). This is because myocardial contraction occurs in response to the depolarization stimulus of an action potential and myocardial relaxation begins during repolarization. The relationships between the electrical activity of the heart, the electrocardiogram, and the cardiac cycle are described in the next section.

CONTROL OF THE HEART RATE

Although the heart's fundamental beat originates within the heart itself, the heart rate can be influenced by the nervous system, hormones, and other factors in the internal environment. The ANS plays a major role in modifying the heart rate according to the need. Sympathetic nervous system stimulation increases the heart rate in response to increased activity. During a fight-or-flight response, the sympathetic nerves can boost the cardiac output on average four to five times the resting value. Sympathetic fibers increase the contraction rate by stimulating the SA and AV nodes. They also increase the contraction force by acting directly on the fibers of the myocardium. These actions translate into increased cardiac output. Parasympathetic stimulation decreases the heart rate to restore homeostasis. The parasympathetic nerve that supplies the heart is the vagus nerve (cranial nerve X). It slows the heart rate by acting on the SA and AV nodes.

These ANS influences allow the heart to meet changing needs rapidly. The heart rate is also affected by substances circulating in the blood, including hormones, such as epinephrine and thyroxine; ions, primarily K+, Na+, and Ca2+; and drugs. Regular exercise strengthens the heart and increases the amount of blood ejected with each beat. Consequently, the body's circulatory needs at rest can be met with a lower heart rate. Trained athletes usually have a low resting heart rate. The following variations in heart rate occur commonly. Note that these variations do not necessarily indicate pathology:

■ **Bradycardia** is a relatively slow heart rate of less than 60 beats/min. During rest and sleep, the heart may beat less than 60 beats/min, but the rate usually does not fall below 50 beats/min.

■ **Tachycardia** refers to a heart rate of more than 100 beats/min. Tachycardia is normal during exercise or stress, or with excessive caffeine intake, but may also occur with certain disorders.

■ **Sinus arrhythmia** is a regular variation in heart rate caused by changes in the rate and depth of breathing. It is a normal phenomenon.

■ **Premature beat**, also called *extrasystole*, is a beat that comes before the expected normal beat. In healthy people, premature beats may be initiated by caffeine, nicotine, or psychologic stresses. They are also common in people with heart disease

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THE RESPIRATORY SYSTEM

The respiratory system is divided into a **respiratory zone**, which is the site of gas exchange between air and blood, and a **conducting zone**. The exchange of gases between air and blood occurs across the walls of pulmonary alveoli, which permit rapid rates of gas diffusion.

LEARNING OUTCOMES

After studying this section, you should be able to:

Describe the structures and functions of the conducting and respiratory zones of the lungs.

Describe the location and significance of the pleural membranes.

The term *respiration* includes three separate but related functions: (1) **ventilation** (breathing); (2) **gas exchange,** which occurs between the air and blood in the lungs and between the blood and other tissues of the body; and (3) **oxygen utilization** by the tissues in the energy-liberating reactions of cell respiration. Ventilation and the exchange of gases (oxygen and carbon dioxide) between the air and blood are collectively called *external respiration.* Gas exchange between the blood and other tissues and oxygen utilization by the tissues are collectively known as *internal respiration.*

Ventilation is the mechanical process that moves air into and out of the lungs. Because the oxygen concentration of air is higher in the lungs than in the blood, oxygen diffuses from air to blood. Carbon dioxide, conversely, moves from the blood to the air within the lungs by diffusing down its concentration gradient. As a result of this gas exchange, the

inspired air contains more oxygen and less carbon dioxide than the expired air. More importantly, blood leaving the lungs (in the pulmonary veins) has a higher oxygen and a lower carbon dioxide concentration than the blood delivered to the lungs in the pulmonary arteries.

This is because the lungs function to bring the blood into gaseous equilibrium with the air. Gas exchange between the air and blood occurs entirely by diffusion through lung tissue. This diffusion occurs very rapidly because of the large surface area within the lungs and the very small diffusion distance between blood and air.

Organs and Structures of the Respiratory System

LEARNING OBJECTIVES

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 CO2
- 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 1).

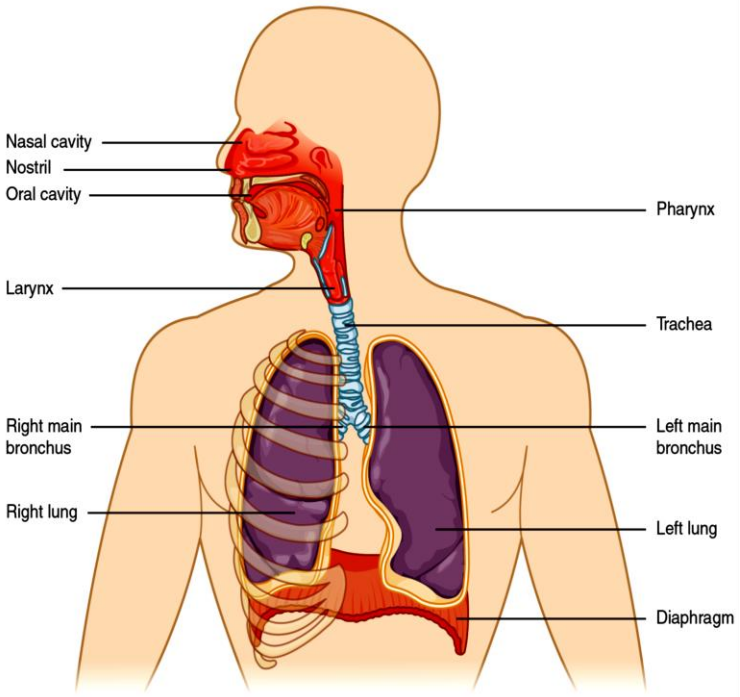

FIGURE 1 Major Respiratory Structures The major respiratory structures span the nasal cavity to the diaphragm.

Gas exchange in each lung occurs across an estimated 300 million tiny (about 100 μm in diameter) air sacs known as **pulmonary alveoli.** The diffusion rate between the alveolar air and capillary blood also depends on the distance separating them. The thickness of the average alveolar cell and capillary endothelial cells is about 0.15 μm each, forming an extremely thin air-blood distance of only about 0.3 μm.

There are two types of alveolar cells, designated **type I alveolar cells** and **type II alveolar cells**. The type I alveolar cells comprise 95% to 97% of the total surface area of the lung; gas exchange with the blood thus occurs primarily through type I alveolar cells. These cells are accordingly very thin. The type II alveolar cells are the cells that secrete pulmonary surfactant (discussed later in this section) and that reabsorb Na+ and H2O, thereby preventing fluid buildup within the alveoli.

In order to maximize the rate of gas diffusion between the air and blood, the air-blood barrier provided by the alveoli is extremely thin and has a very large surface area.

The air passages of the respiratory system are divided into two functional zones. The **respiratory zone** is the region where gas exchange occurs, and it therefore includes the respiratory bronchioles (because they contain separate outpouchings of alveoli) and the terminal alveolar sacs. The **conducting zone** includes all of the anatomical structures through which air passes before reaching the respiratory zone (fig. 2). Air enters the respiratory bronchioles from *terminal bronchioles*, which are the narrowest of the airways that do not have alveoli and do not contribute to gas exchange. The terminal bronchioles receive air from larger airways, which are formed from successive branching's of the *right* and *left primary bronchi.* These two large air passages, in turn, are continuous with the *trachea*, or windpipe, which is located in the neck in front of the esophagus (a muscular tube that carries food to the stomach). The trachea is a sturdy tube supported by rings of cartilage.

Air enters the trachea from the *pharynx*, which is the cavity behind the palate that receives the contents of both the oral and nasal passages. In order for air to enter or leave the trachea and lungs, however, it must pass through a valve like opening called the *glottis* between the vocal folds. The ventricular and vocal folds are part of the *larynx,* or voice box, which

guards the entrance to the trachea. The largest cartilage of the larynx forms the projection at the front of the throat, commonly called the “Adam ’s apple,”.

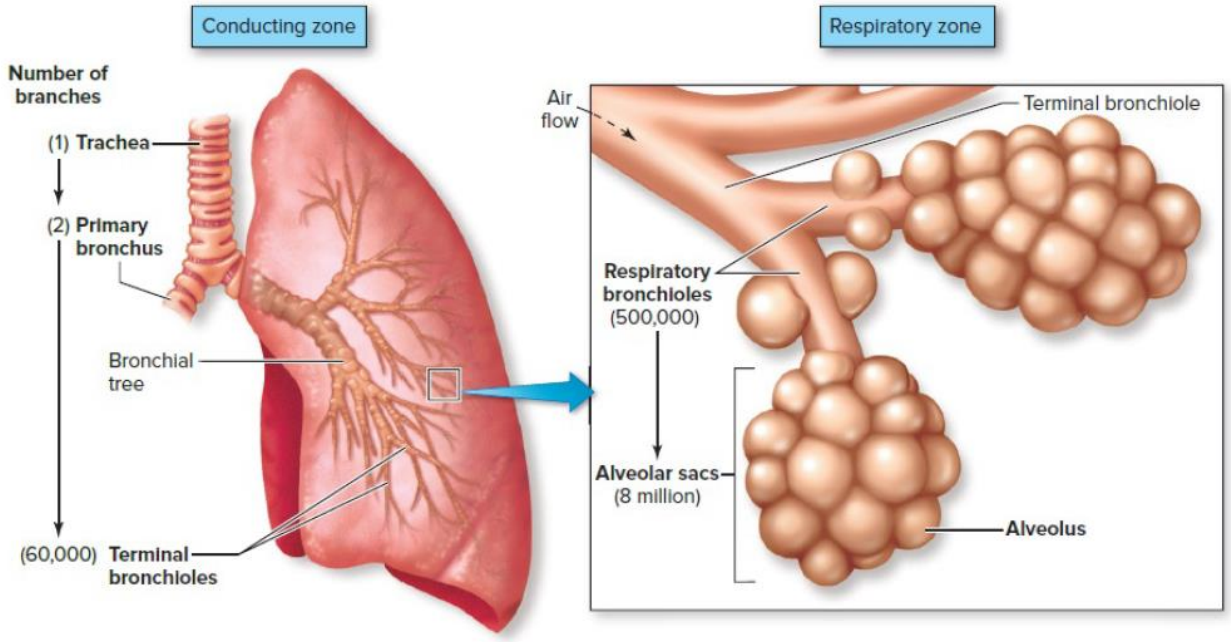

FIGURE 2 The conducting and respiratory zones of the respiratory system. The conducting zone consists of airways that conduct the air to the respiratory zone, which is the region where gas exchange occurs.

The conducting zone of the respiratory system, in summary, consists of the mouth, nose, pharynx, larynx, trachea, primary bronchi, and all successive branching’s of the bronchioles up to and including the terminal bronchioles. In addition to conducting air into the respiratory zone, these structures serve additional functions: *warming* and *humidification* of the inspired air, and *filtration* and *cleaning.*

Regardless of the temperature and humidity of the ambient air, when the inspired air reaches the respiratory zone it is at a temperature of 37° C (body temperature), and it is saturated with water vapor as it flows over the warm, wet mucous membranes that line the respiratory airways.

This mucus is moved along at a rate of 1 to 2 cm per minute by cilia projecting from the tops of epithelial cells that line the conducting zone. There are about 300 cilia per cell that beat in a coordinated fashion as a *mucociliary escalator* to propel the mucus toward the

pharynx, where it can be cleared by swallowing or expectorating. This process is called **mucociliary clearance**.

In *cystic fibrosis* , the mucociliary escalator fails to function properly. This is because of reduced secretion of Cl−, perhaps together with increased absorption of Na+, that leads to mucus with a reduced water content that is too thick for the cilia to properly clear. Also, cigarette smoking has been shown to damage cilia and reduce mucociliary clearance.

As a result of this filtration function, particles larger than about 6 μm do not normally enter the respiratory zone of the lungs. The importance of this function is evidenced by *black lung,* a disease that occurs in miners who inhale large amounts of tiny carbon dust particles from coal, which causes them to develop pulmonary fibrosis. The alveoli themselves are normally kept clean by the action of resident macrophages, which may engulf the carbon dust.

Pulmonary Function Tests

Pulmonary function may be assessed clinically by means of a technique known as *spirometry*. In this procedure, a subject breathes in a closed system in which air is trapped within a light plastic bell floating in water. The bell moves up when the subject exhales and down when the subject inhales. The movements of the bell cause corresponding movements of a pen, which traces a record of the breathing called a *spirogram*. However, computerized devices are now more commonly employed to assess lung function.

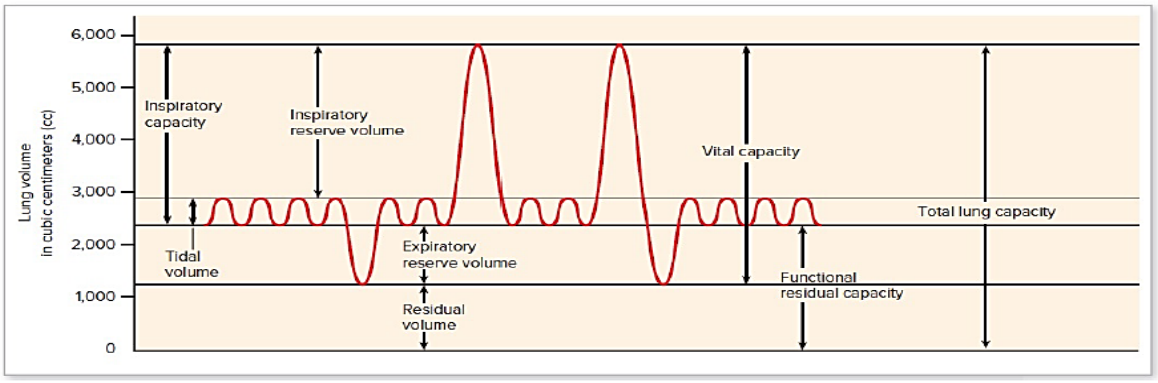

FIGURE 16.15 A spirogram showing lung volumes and capacities. A lung capacity is the sum of two or more lung volumes. The vital capacity, for example, is the sum of the tidal volume, the inspiratory reserve volume, and the expiratory reserve volume. Note that residual volume cannot be measured with a spirometer because it is air that cannot be exhaled. Therefore, the total lung capacity (the sum of the vital capacity and the residual volume) also cannot be measured with a spirometer.

Lung Volumes and Capacities

An example of a spirogram is shown in figure 16.15, and the various lung volumes and capacities are defined in table 16.1, 2. A lung capacity is equal to the sum of two or more lung volumes. During quiet breathing, for example, the amount of air expired in each breath is the **tidal volume.** The maximum amount of air that can be forcefully exhaled after a maximum inhalation is called the **vital capacity,** which is equal to the sum of the **inspiratory reserve volume, tidal volume,** and **expiratory reserve volume**.

TABLE 1 | Mechanisms Involved in Normal, Quiet Ventilation and Forced Ventilation

	Inspiration	Expiration
Normal, Quiet Breathing	Contraction of the diaphragm and external intercostal muscles increases the thoracic and lung volume, decreasing intrapulmonary pressure to about −1 cmH_2O.	Relaxation of the diaphragm and external intercostals, plus elastic recoil of lungs, decreases lung volume and increases intrapulmonary pressure to about +1 cmH_2O.
Forced Ventilation	Inspiration, aided by contraction of accessory muscles such as the scalenes and sternocleidomastoid, decreases intrapulmonary pressure to −27 cmH_2O or lower.	Expiration, aided by contraction of abdominal muscles and internal intercostal muscles, increases intrapulmonary pressure to +40 cmH_2O or higher.

TABLE 16.3 | Terms Used to Describe Lung Volumes and Capacities

Term	Definition
Lung Volumes	The four nonoverlapping components of the total lung capacity
Tidal volume	The volume of gas inspired or expired in an unforced respiratory cycle
Inspiratory reserve volume	The maximum volume of gas that can be inspired during forced breathing in addition to tidal volume
Expiratory reserve volume	The maximum volume of gas that can be expired during forced breathing in addition to tidal volume
Residual volume	The volume of gas remaining in the lungs after a maximum expiration
Lung Capacities	Measurements that are the sum of two or more lung volumes
Total lung capacity	The total amount of gas in the lungs after a maximum inspiration
Vital capacity	The maximum amount of gas that can be expired after a maximum inspiration
Inspiratory capacity	The maximum amount of gas that can be inspired after a normal tidal expiration
Functional residual capacity	The amount of gas remaining in the lungs after a normal tidal expiration

The **residual volume** is the volume of air you cannot expire, even after a maximum forced expiration. This air remains in the lungs because the alveoli and bronchioles normally do not collapse (and the larger airways are non-collapsible). The expiratory reserve volume is the additional air left in the lungs after an unforced expiration. The sum of the residual volume and expiratory reserve volume is known as the **functional residual capacity** (**FRC**).

Not all of the inspired volume reaches the alveoli with each breath. As fresh air is inhaled, it is mixed with air in the **anatomical dead space** (see table 2).

This dead space comprises the conducting zone of the respiratory system—nose, mouth, larynx, trachea, bronchi, and bronchioles—where no gas exchange occurs. Air within the anatomical dead space has a lower oxygen concentration and a higher carbon dioxide concentration than the external air. The air in the dead space enters the alveoli first, so the amount of fresh air reaching the alveoli with each breath is less than the tidal volume. But because the volume of air in the dead space is an anatomical constant, the percentage of fresh air entering the alveoli is increased with increasing tidal volumes. For example, if the anatomical dead space is 150 ml and the tidal volume is 500 ml, the percentage of fresh air reaching the alveoli is 350/500 × 100% = 70%. If the tidal volume is increased to 2,000 ml, and the anatomical dead space is still 150 ml, the percentage of fresh air reaching the alveoli is increased to 1,850/2,000 × 100% = 93%. An increase in tidal volume can thus be a factor in the respiratory adaptations to exercise and high altitude.

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Hypoxia

Objectives:

- Review the various etiologies of hypoxia.
- Describe the presentation of a patient with hypoxia.
- Outline the management options available for hypoxia.
- Identify interprofessional team strategies for improving care coordination and outcomes in patients with hypoxia

Hypoxia is defined as a deficiency of oxygen at the tissue level. There are many potential causes of hypoxia, but they can be classified into four general categories:

(1) hypoxic hypoxia (also termed hypoxemia), in which the arterial PO2 is reduced;

(2) anemic hypoxia or carbon monoxide hypoxia, in which the arterial PO2 is normal but the total oxygen content of the blood is decreased because of inadequate numbers of erythrocytes, deficient or abnormal hemoglobin, or competition for the hemoglobin molecule by carbon monoxide (see Figure 13.29);

(3) ischemic hypoxia (also called hypoperfusion hypoxia), in which blood flow to the tissues is too low; and

(4) ***histotoxic hypoxia,*** in which the quantity of oxygen reaching the tissues is normal but the cell is unable to utilize the oxygen because a toxic agent−cyanide, for example−has interfered with the cell' s metabolic machinery.

The hypoxemic type of hypoxia is due to one of two mechanisms:

(1) a decrease in the amount of breathable oxygen—often encountered in pilots, mountain climbers, and people living at high altitudes—due to reduced barometric pressure or

(2) cardiopulmonary failure in which the lungs are unable to efficiently transfer oxygen from the alveoli to the blood.

❖ In the case of anemic hypoxia, either the total amount of hemoglobin is too small to supply the body's oxygen needs, as in anemia or after severe bleeding, or hemoglobin that is present is rendered nonfunctional.

Examples of the latter case are carbon monoxide poisoning and acquired methemoglobinemia, in both of which the hemoglobin is so

altered by toxic agents that it becomes unavailable for oxygen transport, and thus of no respiratory value.

- Stagnant hypoxia, in which blood flow through the capillaries is insufficient to supply the tissues, may be general or local. If general, it may result from heart disease that impairs the circulation, impairment of veinous return of blood, or trauma that induces shock. Local stagnant hypoxia may be due to any condition that reduces or prevents the circulation of the blood in any area of the body.

  Examples include Raynaud syndrome and Buerger disease, which restrict circulation in the extremities; the application of a tourniquet to control bleeding; ergot poisoning; exposure to cold; and overwhelming systemic infection with shock.

- In histotoxic hypoxia the cells of the body are unable to use the oxygen, although the amount in the blood may be normal and under normal tension. Although characteristically produced by cyanide, any agent that decreases cellular respiration may cause it. Some of these agents are narcotics, alcohol, formaldehyde, acetone, and certain anesthetic agents.

The following is a descriptive classification of the causes of hypoxia:

1. Inadequate oxygenation of the blood in the lungs because of extrinsic reasons

a. Deficiency of O2 in the atmosphere

b. Hypoventilation (neuromuscular disorders)

2. Pulmonary disease

a. Hypoventilation caused by increased airway resistance or decreased pulmonary compliance

b. Abnormal alveolar ventilation-perfusion ratio (including increased physiological dead space or increased physiological shunt)

A shunt is an anatomical abnormality of the cardiovascular system that causes mixed venous blood to bypass ventilated alveoli in passing from the right side of the heart to the left side.

c. Diminished respiratory membrane diffusion

3. Venous-to- arterial shunts (right-to- left cardiac shunts)

4. Inadequate O2 transport to the tissues by the blood

a. Anemia or abnormal hemoglobin

b. General circulatory deficiency

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

d. Tissue edema

5. Inadequate tissue capability of using O2

a. Poisoning of cellular oxidation enzymes

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

This classification of the types of hypoxia is mainly self-evident from the discussions earlier in the chapter. Only one type of hypoxia in the classification needs further elaboration—the hypoxia caused by inadequate capability of the body's tissue cells to use O2.

Anoxia

Anoxia is a condition of complete oxygen deficiency in the body. This causes body tissues or organs to malfunction, thereby leading to serious health complications. If not treated promptly, anoxia can be fatal.

What Is Anoxia?

As previously stated, anoxia is a complete lack of oxygen in the body. This condition is considered a medical emergency. To maintain adequate oxygen levels in the blood, there are three physiological processes needed: perfusion, ventilation, and diffusion. If one process is disrupted, a lack of oxygen can occur.

Anoxia is different from hypoxia. Anoxia is a condition marked by a total lack of oxygen in the body, while hypoxia refers to a decrease in oxygen levels to below the normal range. In hypoxia, the body still receives oxygen, but the amount of oxygen is not sufficient to support proper bodily functions.

Anoxia can trigger serious health complications, such as brain damage and organ failure. For instance, a complete lack of oxygen to the brain can result in a stroke. Meanwhile, inadequate oxygen distribution can cause organ failure, such as heart failure and kidney failure, decreasing consciousness, and others.

Types of Anoxia

In general, there are four common types of anoxia in the medical field: anoxic anoxia, anemic anoxia, stagnant anoxia, and toxic anoxia. Here are the details:

- ✓ Anoxic anoxia: Lacks of oxygen due to insufficient oxygen levels in the air, such as when hiking mountains.
- ✓ Anemic anoxia: Red blood cells are not able to carry enough oxygen, either due to inadequate hemoglobin levels or changes in hemoglobin capacity as an oxygen distributor. This condition is also caused by a deficiency in red blood cells, which are also typically associated with chronic anemia, pulmonary disorders, acute bleeding, and others.
- ✓ Stagnant anoxia: This anoxia occurs when the blood fails to receive oxygen and is not distributed well. It is commonly caused by arrhythmia, heart attack, and stroke.
- ✓ Toxic anoxia: This happens when toxic substances are found in the body, such as carbon monoxide, narcotics, or alcohol in the body, interfering with oxygen distribution to the tissue of body organs.

Causes of Anoxia

Anoxia is primarily caused by an inadequate supply of oxygenated blood to the organs and tissues. This condition is a medical emergency that requires immediate treatment because insufficient oxygen can damage the brain and vital organs within minutes. Early intervention can be crucial in saving the life of patients with anoxia.

Symptoms of Anoxia

Anoxia has similar symptoms to hypoxia. Both conditions are marked by a lack of oxygen in the body. The severity depends on the duration and levels of oxygen deficiency. Several anoxia symptoms that warrant caution are:

Shortness of breath or difficulty breathing, Confusion, Restlessness, Headache, Cyanosis, Palpitations, Seizures, Loss of consciousness or fainting, Signs of brain damage.

Effects of Hypoxia on the Body

Hypoxia, if severe enough, can cause death of cells throughout the body, but in less severe degrees, it mainly causes (1) depressed mental activity, sometimes culminating in coma, and (2) reduced work capacity of the muscles.

- In hypoxia caused by impaired alveolar membrane diffusion, essentially the same result occurs as in hypoventilation hypoxia because O2 therapy can increase the Po2 in the lung alveoli from the normal value of about 100 mm Hg to as high as 600 mm Hg.
- In hypoxia caused by anemia, abnormal hemoglobin transport of O2, circulatory deficiency, or physiological shunt, O2 therapy is of much less value because normal O2 is already available in the alveoli. Instead, the problem is that one or more of the mechanisms for transporting oxygen from the lungs to the tissues are deficient.
- In the different types of hypoxia caused by inadequate tissue use of O2, there is no abnormality of O2 pickup by the lungs or of transport to the tissues. Instead, the tissue metabolic enzyme system is simply incapable of using the O2 that is delivered. Therefore, O2 therapy provides no measurable benefit.

ACUTE EFFECTS OF HYPOXIA

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

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

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THE NERVOUS SYSTEM

NEURONS AND SUPPORTING CELLS

The nervous system is composed of neurons, which produce and conduct electrochemical impulses, and supporting cells, which assist the functions of neurons. Neurons are classified functionally and structurally; the various types of supporting cells perform specialized functions.

LEARNING OUTCOMES

After studying this section, you should be able to:

1. Describe the different types of neurons and supporting cells, and identify their functions.
2. Identify the myelin sheath and describe how it is formed in the CNS and PNS.

The nervous system is divided into the **central nervous system (CNS),** which the brain and spinal cord, and the **peripheral nervous system (PNS),** which includes the *cranial nerves* arising from the brain and the *spinal nerves* arising from the spinal cord.

The nervous system is composed of only two principal types of cells neurons and supporting cells. **Neurons** are the basic structural and functional units of the nervous system. They are specialized to respond to physical and chemical stimuli, conduct electrochemical impulses, and release chemical regulators. Through these activities, neurons enable the perception of sensory stimuli, learning, memory, and the control of muscles and glands. Most neurons cannot divide by mitosis, although many can regenerate a severed portion or sprout small new branches under certain conditions.

Supporting cells aid the functions of neurons and are about five times more abundant than neurons. In common usage, supporting cells are collectively called **neuroglia** (from the Middle Greek *glia* = glue). Unlike neurons, which do not divide mitotically (except for particular neural stem cells), neuroglia are able to divide by mitosis. This helps to explain why brain tumors in adults are usually composed of neuroglia rather than of neurons.

Neurons

Although neurons vary considerably in size and shape, they generally have three principal regions: (1) a cell body, (2) dendrites, and (3) an axon (figs. 7.1 and 7.2). Dendrites and axons can be referred to generically as *processes*, or extensions from the cell body.

The **cell body** is the enlarged portion of the neuron that contains the nucleus. It is the "nutritional center" of the neuron where macromolecules are produced. The cell body and larger dendrites (but not axons) contain *Nissl bodies*, which are seen as dark-staining granules under the microscope. Nissl bodies are composed of large stacks of rough endoplasmic reticulum that are needed for the synthesis of membrane proteins. The cell bodies within the CNS are frequently clustered into groups called *nuclei* (not to be confused with the nucleus of a cell). Cell bodies in the PNS usually occur in clusters called *ganglia* (table 7.1).

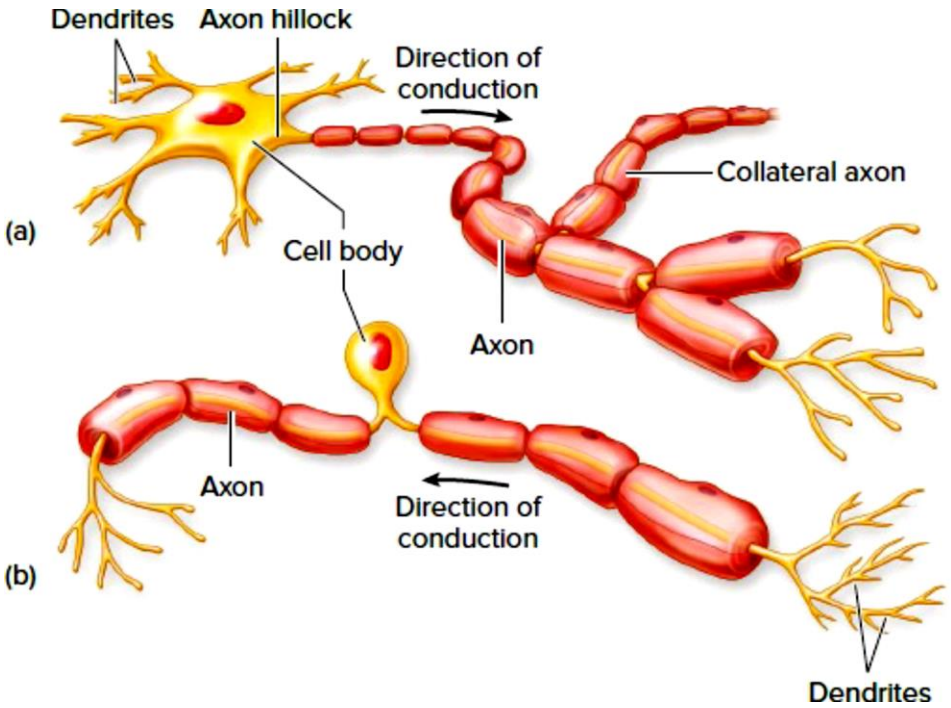

FIGURE 7.1 The structure of two kinds of neurons. A motor neuron (*a*) and a sensory neuron (*b*) are depicted here

Dendrites (from the Greek *dendron* = tree branch) are thin, branched processes that extend from the cytoplasm of the cell body. Dendrites provide a receptive area that transmits graded electrochemical impulses to the cell body. The **axon** is a longer process that conducts impulses, called *action potentials* (section 7.2), away from the cell body. The origin of the axon near the cell body is an expanded region called the *axon hillock.*

Axons vary in length from only a millimeter long to over a meter or more in length (for axons that extend from the CNS to the foot). Toward their ends, axons can produce up to 200 or more branches called **axon collaterals,** and each of these can divide to synapse with many other neurons. In this way, a single CNS axon may synapse with as many as 30,000 to 60,000 other neurons. Because axons can be quite long, special mechanisms are required to transport organelles and proteins from the cell body to the end of the axon. This **axonal transport** is energy-dependent and is often divided into a *fast component* and two *slow components.* The fast component (at 200 to 400 mm/day) mainly transports membranous vesicles (important for synaptic transmission, as discussed in section 7.3). One slow component (at 0.2 to 1 mm/day) transports microfilaments and microtubules of the cytoskeleton; the other slow component (at 2 to 8 mm/day) transports more than 200 different proteins, including those critical for synaptic function. The slow components appear to transport their cargo in fast bursts with frequent pauses, so that the overall rate of transport is much slower than that occurring in the fast component.

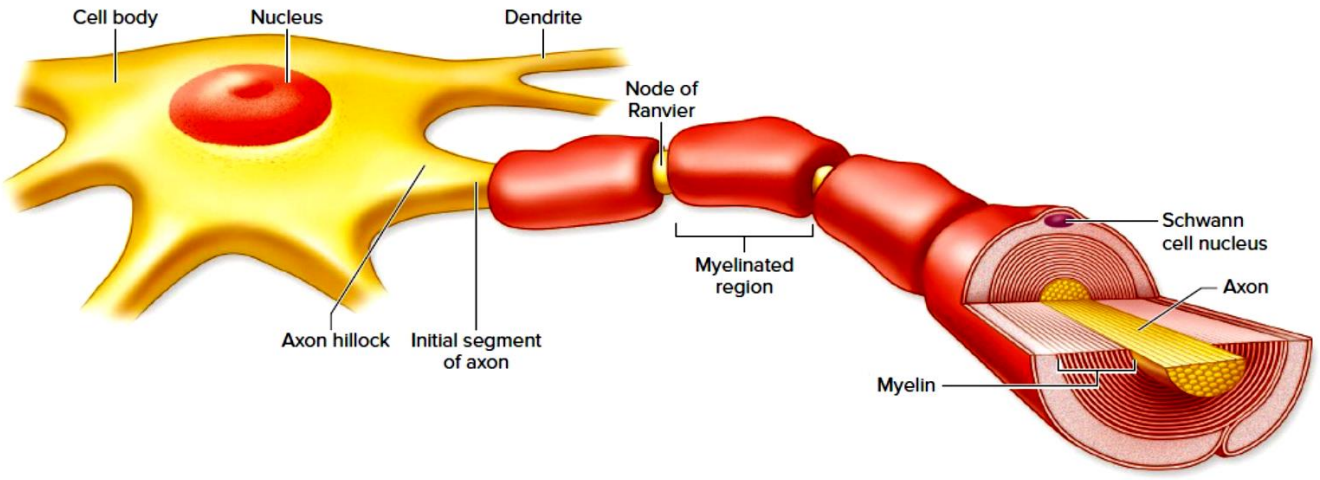

FIGURE 7.2 Parts of a neuron. The axon of this neuron is wrapped by Schwann cells, which form a myelin sheath. The myelin sheath is an insulating layer that increases the speed of nerve impulse conduction.

TABLE 7.1 | Terminology Pertaining to the Nervous System

Term	Definition
Central nervous system (CNS)	Brain and spinal cord
Peripheral nervous system (PNS)	Nerves, ganglia, and nerve plexuses (outside of the CNS)
Interneuron	Multipolar neuron located entirely within the CNS
Sensory neuron (afferent neuron)	Neuron that transmits impulses from a sensory receptor into the CNS
Motor neuron (efferent neuron)	Neuron that transmits impulses from the CNS to an effector organ; for example, a muscle
Nerve	Cablelike collection of many axons in the PNS; may be "mixed" (contain both sensory and motor fibers)
Somatic motor nerve	Nerve that stimulates contraction of skeletal muscles
Autonomic motor nerve	Nerve that stimulates contraction (or inhibits contraction) of smooth muscle and cardiac muscle and that stimulates glandular secretion
Ganglion	Grouping of neuron cell bodies located outside the CNS
Nucleus	Grouping of neuron cell bodies within the CNS
Tract	Grouping of axons that interconnect regions of the CNS

Axonal transport may occur from the cell body to the axon and dendrites. This direction is called **anterograde transport,** and involves molecular motors of *kinesin* proteins that move cargo along the microtubules of the cytoskeleton. For example, kinesin motors move synaptic vesicles, mitochondria, and ion channels from the cell body through the axon. Similar anterograde transport occurs in the dendrites, as kinesin moves postsynaptic receptors for neurotransmitters and ion channels along the microtubules in the dendrites.

By contrast, axonal transport in the opposite direction—that is, along the axon and dendrites toward the cell body—is known as **retrograde transport.** This involves the motor protein *dynein* and its activator,

dynactin. These molecular motors carry lysosomes, autophagosomes, endosomes, and various molecules along microtubules of the cytoskeleton toward the cell body of the neuron.
Retrograde transport can also be responsible for movement of herpes virus, rabies virus, and tetanus toxin from the end of the axon into cell bodies.

Neuroglia

Unlike other organs that are "packaged" in connective tissue derived from mesoderm (the middle layer of embryonic tissue), most of the supporting cells of the nervous system are derived from the same embryonic tissue layer (ectoderm) that produces neurons. The term *neuroglia* traditionally refers to the supporting cells of the CNS, but in current usage the supporting cells of the PNS are often also classified as neuroglia.
There are two types of neuroglia in the peripheral nervous system:

1. **Schwann cells,** which form myelin sheaths around peripheral axons; and
2. **satellite cells,** which support neuron cell bodies within the ganglia of the PNS.

There are four types of neuroglia in the central nervous system (fig. 7.5):

1. **oligodendrocytes,** which form myelin sheaths around axons of the CNS;
2. **microglia,** which migrate through the CNS and phagocytose foreign and degenerated material;
3. **astrocytes,** which help to regulate the external environment of neurons in the CNS; and
4. **ependymal cells,** which are epithelial cells that line the ventricles (cavities) of the brain and the central canal of the spinal cord.

The functions of the other neuroglia are described later in this section and summarized in table 7.2.

TABLE 7.2 | Neuroglia and Their Functions

Cell Type	Location	Functions
Schwann cells	PNS Also called neurolemmocytes,	produce the myelin sheaths around the myelinated axons of the peripheral nervous system; surround all PNS axons (myelinated and nonmyelinated) to form a neurilemmal sheath
Satellite cells	PNS Support	functions of neurons within sensory and autonomic ganglia
Oligodendrocytes	CNS	Form myelin sheaths around central axons, producing "white matter" of the CNS
Microglia	CNS	Phagocytose pathogens and cellular debris in the CNS
Astrocytes	CNS	Cover capillaries of the CNS and induce the blood-brain barrier; interact metabolically with neurons and modify the extracellular environment of neurons
Ependymal cells	CNS	Form the epithelial lining of brain cavities (ventricles) and the central canal of the spinal cord; cover tufts of capillaries to form choroid plexuses–structures that produce cerebrospinal fluid

PHYSIOLOGY

Assist. Prof. Dr. Fatimah A Jasim

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VANDER′ S Human Physiology 15th ed. By ERIC P. WIDMAIER

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Central Nervous System

STRUCTURAL ORGANIZATION OF THE BRAIN

LEARNING OBJECTIVES

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

- Name the major regions of the adult brain
- Describe the connections between the cerebrum and brain stem through the diencephalon, and from those regions into the spinal cord
- Recognize the complex connections within the subcortical structures of the basal nuclei
- Explain the arrangement of gray and white matter in the spinal cord

The brain and the spinal cord are the central nervous system, and they represent the main organs of the nervous system. The spinal cord is a single structure, whereas the adult brain is described in terms of four major regions: the cerebrum, the diencephalon, the brain stem, and the cerebellum. A person' s conscious experiences are based on neural activity in the brain. The regulation of homeostasis is governed by a specialized region in the brain. The coordination of reflexes depends on the integration of sensory and motor pathways in the spinal cord.

The Cerebrum

The iconic gray mantle of the human brain, which appears to make up most of the mass of the brain, is the **cerebrum** (Figure 9.1). The wrinkled portion is the **cerebral cortex**, and the rest of the structure is beneath that outer covering. There is a large separation between the two sides of the cerebrum called the **longitudinal fissure**. It separates the cerebrum into two distinct halves, a right and left **cerebral hemisphere**. Deep within the cerebrum, the white matter of the **corpus callosum** provides the major pathway for communication between the two hemispheres of the cerebral cortex.

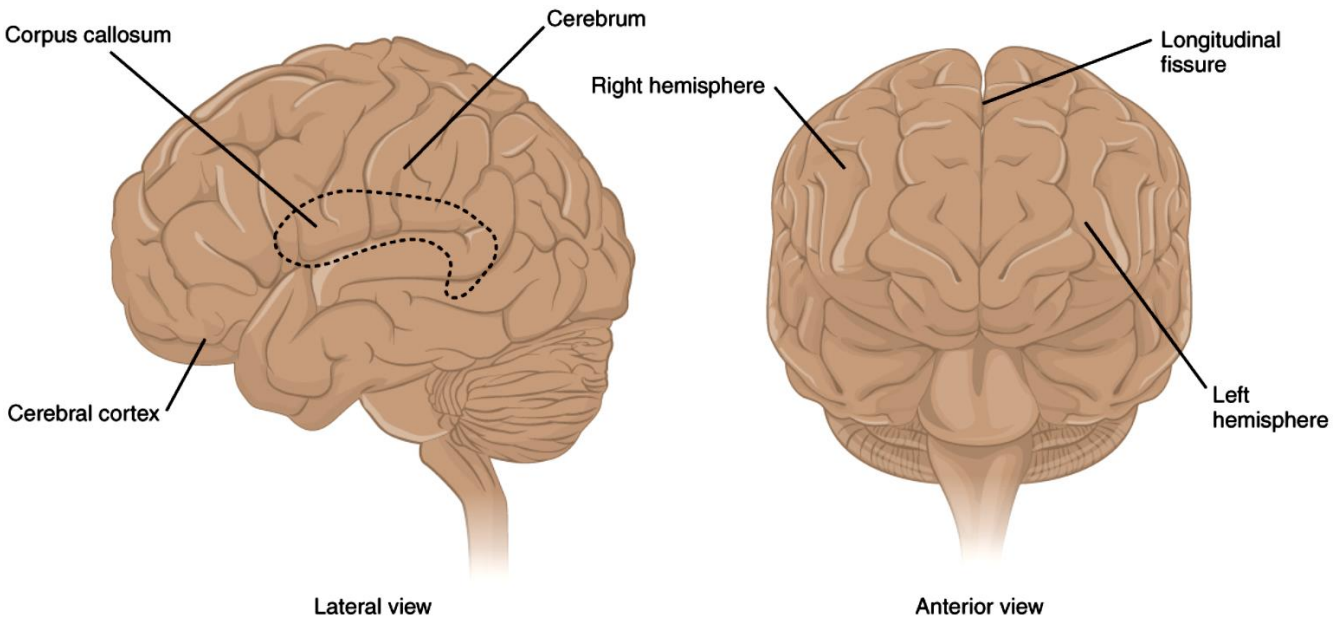

FIGURE 9.1 The Cerebrum The cerebrum is a large component of the CNS in humans, and the most obvious aspect of it is the folded surface called the cerebral cortex.

Many of the higher neurological functions, such as memory, emotion, and consciousness, are the result of cerebral function. The complexity of the cerebrum is different across vertebrate species. The cerebrum of the most primitive vertebrates is not much more than the connection for the sense of smell. In mammals, the cerebrum comprises the outer gray matter that is the cortex (from the Latin word meaning "bark of a tree") and several deep nuclei that belong to three important functional groups. The **basal nuclei** are responsible for cognitive processing, the most important function being that associated with planning movements. The **basal forebrain** contains nuclei that are important in learning and memory. The **limbic cortex** is the region of the cerebral cortex that is part of the **limbic system**, a collection of structures involved in emotion, memory, and behavior.

CEREBRUM

The cerebrum, consisting of five paired lobes within two convoluted hemispheres, contains grey matter in its cortex and in deeper cerebral nuclei. Most of what are considered to be the higher functions of the brain are performed by the cerebrum.

LEARNING OUTCOMES

After studying this section, you should be able to:

- Distinguish between the functions of the right and left cerebral hemispheres, and describe the significance of the limbic system.
- Identify the areas of cerebral cortex.

The **cerebrum** (fig. 9.2), which is the only structure of the telencephalon, is the largest portion of the brain (accounting for about 80% of its mass) and is the brain region primarily responsible for higher mental functions. The cerebrum consists of *right* and *left hemispheres*, which are connected internally by a large fiber tract called the *corpus callosum* (see fig. 9.2).

The corpus callosum is the major tract of axons that functionally interconnects the right and left cerebral hemispheres. grey matter (with mostly cell bodies and dendrites) and underlying white matter (consisting of mostly myelinated axons).

The cerebral cortex is characterized by numerous folds and grooves called ***convolutions***. An elevated fold of a convolution is called a ***gyrus*** (plural: *gyri*), and the depressed groove between two gyri is a ***sulcus*** (plural: *sulci*).

Each cerebral hemisphere is subdivided by deep sulci, or ***fissures***, into five lobes, four of which are visible from the surface (fig. 8.6). These lobes are the *frontal*, *parietal*, *temporal*, and *occipital*, which are visible from the surface, and the deep *insula*, which is covered by portions of the frontal, parietal, and temporal lobes (table 9.1). Scientists have recently identified 180 separate structural and functional compartments in the lobes of each cerebral hemisphere. This number will likely be increased through future studies.

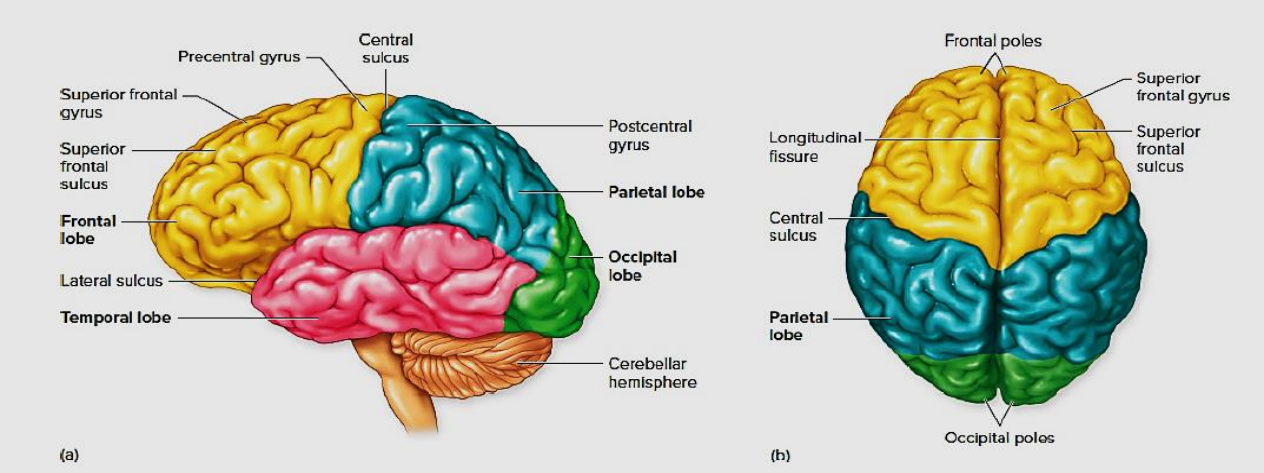

FIGURE 9.2 The cerebrum. (*a*) A lateral view and (*b*) a superior view.

The **frontal lobe** is the anterior portion of each cerebral hemisphere. A deep fissure, called the *central sulcus*, separates the frontal lobe from the **parietal lobe.** The *precentral gyrus* (figs. 9.2), involved in motor control, is located in the frontal lobe just in front of the central sulcus.

The **temporal lobe** contains auditory centers that receive sensory fibers from the cochlea of each ear. This lobe is also involved in the interpretation and association of auditory and visual information. The **occipital lobe** is the primary area responsible for vision and for the coordination of eye movements.

The **insula** (fig. 9.2) is implicated in the encoding of memory and in the integration of sensory information with visceral responses.

TABLE 8.1 | Functions of the Cerebral Lobes

Lobe	Functions
Frontal	Voluntary motor control of skeletal muscles; personality; higher intellectual processes (e.g., concentration, planning, and decision making); verbal communication
Parietal	Somatesthetic interpretation (e.g., cutaneous and muscular sensations); understanding speech and formulating words to express thoughts and emotions; interpretation of textures and shapes
Temporal	Interpretation of auditory sensations; storage (memory) of auditory and visual experiences
Occipital	Integration of movements in focusing the eye; correlation of visual images with previous visual experiences and other sensory stimuli; conscious perception of vision
Insula	Memory; sensory (principally pain) and visceral integration

CEREBELLUM

The **cerebellum** is made up of three parts: the middle portion (vermis) and two lateral hemispheres, the left and right. Like the cerebral hemispheres, the cerebellum has an outer area of gray matter and an inner portion that is largely white matter **(see Fig. 9.3)**. However, the white matter is distributed in a treelike pattern. The functions of the cerebellum are as follows:

■ Help coordinate voluntary muscles to ensure smooth, orderly function. Disease of the cerebellum causes muscular jerkiness and tremors.

■ Help maintain balance in standing, walking, and sitting as well as during more strenuous activities. Messages from the internal ear and from sensory receptors in tendons and muscles aid the cerebellum.

■ Help maintain muscle tone so that all muscle fibers are slightly tensed and ready to produce changes in position as quickly as necessary.

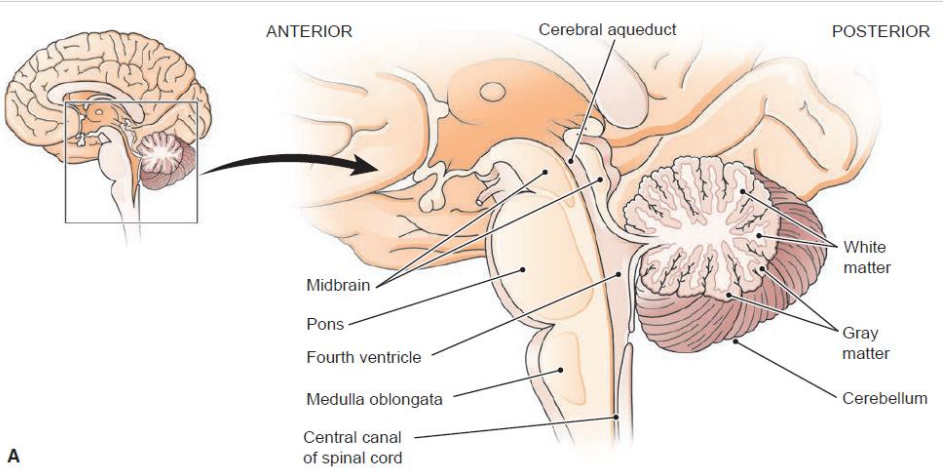

Figure 9-3 The brain stem and cerebellum

The Autonomic Nervous System

NEURAL CONTROL OF INVOLUNTARY EFFECTORS

The autonomic nervous system helps regulate the activities of cardiac muscle, smooth muscles, and glands. In this regulation, impulses are conducted from the CNS by an axon that synapses with a second autonomic neuron. It is the axon of this second neuron in the pathway that innervates the involuntary effectors.

LEARNING OUTCOMES

After studying this section, you should be able to:

- Describe the organization of autonomic motor neurons.
- Describe how neural regulation of smooth and cardiac muscles differs from neural regulation of skeletal muscles.

Autonomic motor nerves innervate organs whose functions are not usually under voluntary control. The effectors that respond to autonomic regulation include **cardiac muscle** (the heart), **smooth muscles,** and **glands.** These effectors are part of the *visceral organs* (organs within the body cavities) and of blood vessels. The involuntary effects of autonomic innervation contrast with the voluntary control of skeletal muscles by way of somatic motor neurons.

Autonomic Neurons Neurons of the peripheral nervous system (PNS) that conduct impulses away from the central nervous system (CNS) are known as *motor*, or *efferent, neurons*. There are two major categories of motor neurons: **somatic** and **autonomic**.

Somatic motor neurons have their cell bodies within the CNS and send axons to skeletal muscles, which are usually under voluntary control. Unlike somatic motor neurons, which conduct impulses along a single axon from the spinal cord to the neuromuscular junction, autonomic motor control involves two neurons in the efferent pathway. The first of these neurons has its cell body in the grey matter of the brain or spinal cord. The axon of this neuron does not directly innervate the effector organ but instead synapses with a second neuron within an *autonomic ganglion* (a ganglion is a collection of cell bodies outside the CNS). The first neuron is thus called a **preganglionic neuron.** The second neuron in this pathway, called a **postganglionic neuron,** has an axon that extends from the autonomic ganglion to an effector organ, where it synapses with its involuntary effector cells (fig. 9.4).

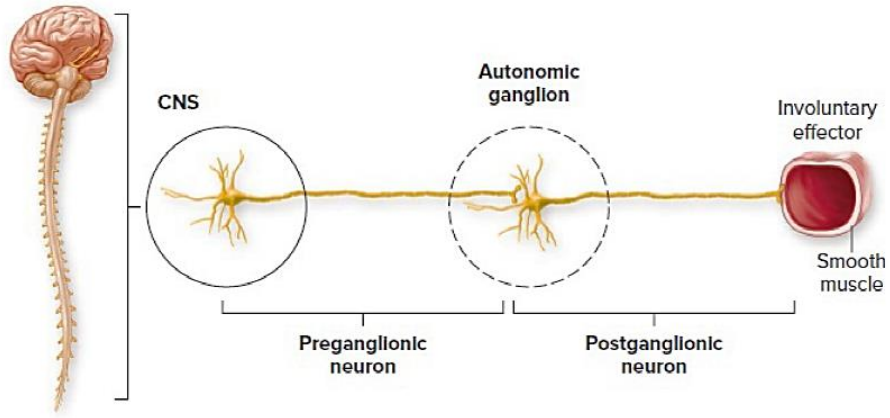

FIGURE 9.4 The autonomic system has preganglionic and postganglionic neurons. The preganglionic neurons of the autonomic system have cell bodies in the CNS, whereas the postganglionic neurons have cell bodies within autonomic ganglia. The sympathetic and parasympathetic divisions differ in the particular locations of their preganglionic neuron cell bodies within the CNS, and in the location of their ganglia.

Preganglionic autonomic fibers originate in the midbrain and hindbrain and in the upper thoracic to the fourth sacral levels of the spinal cord. Autonomic ganglia are located in the head, neck, and abdomen; chains of autonomic ganglia also parallel the right and left sides of the spinal cord. The origin of the preganglionic fibers and the location of the autonomic ganglia help to distinguish the *sympathetic* and *parasympathetic divisions* of the autonomic system.

The sensory neurons that conduct information from the viscera for autonomic nerve reflexes can have the same anatomy as those sensory neurons involved in somatic motor reflexes (table 9.2). That is, the sensory information enters the spinal cord on the dorsal roots of the spinal nerves. However, some important visceral sensory information can instead enter the brain in cranial nerves. For example, information about blood pressure, plasma pH, and oxygen concentration is carried into the brain by sensory axons in cranial nerves IX and X. These are mixed nerves, containing both sensory and parasympathetic motor axons.

TABLE 9.2 | Comparison of the Somatic Motor System and the Autonomic Motor System

Feature	Somatic Motor	Autonomic Motor
Effector organs	Skeletal muscles	Cardiac muscle, smooth muscle, and glands
Presence of ganglia	No ganglia	Cell bodies of postganglionic autonomic fibers located in paravertebral, prevertebral (collateral), and terminal ganglia
Number of neurons from CNS to effector	One	Two
Type of neuromuscular junction	Specialized motor end plate	No specialization of muscle cells postsynaptic membrane; all areas of smooth contain receptor proteins for neurotransmitters
Effect of nerve impulse on muscle	Excitatory only	Either excitatory or inhibitory
Type of nerve fibers	Fast-conducting, thick (9–13 μm), and myelinated	Slow-conducting; preganglionic fibers lightly myelinated but thin (3 μm); postganglionic fibers unmyelinated and very thin (about 1.0 μm)
Effect of	Flaccid paralysis and	Muscle tone and function persist; target cells show denervation

FUNCTIONS OF THE AUTONOMIC NERVOUS SYSTEM

The sympathetic division of the autonomic system activates the body to "fight or flight," largely through the release of norepinephrine from postganglionic neurons and the secretion of epinephrine from the adrenal medulla. The parasympathetic division often produces antagonistic effects through the release of acetylcholine from its postganglionic neurons.

A- The sympathetic division of the autonomic system activates the body to "fight or flight" through adrenergic effects. The parasympathetic division often exerts antagonistic actions through cholinergic effects.

B- All preganglionic autonomic nerve fibers are cholinergic (use ACh as a neurotransmitter).

1. All postganglionic parasympathetic fibers are cholinergic.
2. Most postganglionic sympathetic fibers are adrenergic (use norepinephrine as a neurotransmitter).
3. Sympathetic fibers that innervate sweat glands and those that innervate blood vessels in skeletal muscles are cholinergic.

C. Adrenergic effects include stimulation of the heart, vasoconstriction in the viscera and skin, bronchodilation, and glycogenolysis in the liver.

1. The two main classes of adrenergic receptor proteins are alpha and beta.
2. Some organs have only alpha or only beta receptors; other organs (such as the heart) have both types of receptors.
3. There are two subtypes of alpha receptors (α1 and α2) and two subtypes of beta receptors (β1 and β2). These subtypes can be selectively stimulated or blocked by therapeutic drugs.

D- Cholinergic effects of parasympathetic nerves are promoted by the drug muscarine and inhibited by atropine.

E- In organs with dual innervation, the effects of the sympathetic and parasympathetic divisions can be antagonistic, complementary, or cooperative.

1. The effects are antagonistic in the heart and pupils of the eyes.
2. The effects are complementary in the regulation of salivary gland secretion and are cooperative in the regulation of the reproductive and urinary systems.

F- In organs without dual innervation (such as most blood vessels), regulation is achieved by variations in sympathetic nerve activity.

G- The medulla oblongata of the brain stem is the area that most directly controls the activity of the autonomic system.

1. The medulla oblongata is, in turn, influenced by sensory input and by input from the hypothalamus.
2. The hypothalamus is influenced by input from the limbic system, cerebellum, and cerebrum.
3. These interconnections provide an autonomic component to some of the visceral responses that accompany emotions