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Section 16: The Cardiovascular System: Blood
Learning Objectives

After studying this chapter, 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 chapter focuses on the medium of transport: blood.

A single drop of blood contains millions of red blood cells, white blood cells, and platelets. One of each type is shown in Figure 1, isolated from a scanning electron micrograph.

Figure 1. Blood cell types.

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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 1). 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 1. 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.

The volume of erythrocytes after centrifugation is also commonly referred to as packed cell volume (PCV). In normal blood, about 45 percent of a sample is erythrocytes. The hematocrit of any one sample can vary significantly, however, about 36–50 percent, according to gender and other factors. Normal hematocrit values for females range from 37 to 47, with a mean value of 41; for males, hematocrit ranges from 42 to 52, with a mean of 47. The percentage of other formed elements, the WBCs and platelets, is extremely small so it is not normally considered with the hematocrit. So the mean plasma percentage is the percent of blood that is not erythrocytes: for females, it is approximately 59 (or 100 minus 41), and for males, it is approximately 53 (or 100 minus 47).

**Characteristics of Blood**

When you think about blood, the first characteristic that probably comes to mind is its color. Blood that has just taken up oxygen in the lungs is bright red, and blood that has released oxygen in the tissues is a more dusky red. This is because hemoglobin is a pigment that changes color, depending upon the degree of oxygen saturation.

Blood is viscous and somewhat sticky to the touch. It has a viscosity approximately five times greater than water. Viscosity is a measure of a fluid’s thickness or resistance to flow, and is influenced by the presence of the plasma proteins and formed elements within the blood. The viscosity of blood has a dramatic impact on blood pressure and flow. Consider the difference in flow between water and honey. The more viscous honey would demonstrate a greater resistance to flow than the less viscous water. The same principle applies to blood.

The normal temperature of blood is slightly higher than normal body temperature—about 38 °C (or 100.4 °F), compared to 37 °C (or 98.6 °F) for an internal body temperature reading, although daily variations of 0.5 °C are normal. Although the surface of blood vessels is relatively smooth, as blood flows through them, it experiences some friction and resistance, especially as vessels age and lose their elasticity, thereby producing heat. This accounts for its slightly higher temperature.

The pH of blood averages about 7.4; however, it can range from 7.35 to 7.45 in a healthy person. Blood is therefore somewhat more basic (alkaline) on a chemical scale than pure water, which has a pH of 7.0. Blood contains numerous buffers that actually help to regulate pH.

Blood constitutes approximately 8 percent of adult body weight. Adult males typically average about 5 to 6 liters of blood. Females average 4-5 liters.

**Blood Plasma**

Like other fluids in the body, plasma is composed primarily of water: In fact, it is about 92 percent water. Dissolved or suspended within this water is a mixture of substances, most of which are proteins. There are literally hundreds of substances dissolved or suspended in the plasma, although many of them are found only in very small quantities.

**Practice Question**

Visit the website link in the online textbook for a list of normal levels established for many of the substances found in a sample of blood. Serum, one of the specimen types included, refers to a sample of plasma after clotting factors have been removed. What types of measurements are given for levels of glucose in the blood?
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 major components of plasma are summarized in Table 1.

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.

- The least abundant plasma protein is **fibrinogen**. Like albumin and the alpha and beta globulins, fibrinogen is produced by the liver. It is essential for blood clotting, a process described later in this chapter. 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 nonprotein solutes combined contribute approximately 1 percent to the total volume of plasma.
### Table 1. Major Blood Components

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

Phlebotomists are professionals trained to draw blood (phleb- = “a blood vessel”; -tomy = “to cut”). When more than a few drops of blood are required, phlebotomists perform a venipuncture, typically of a surface vein in the arm. They perform a capillary stick on a finger, an earlobe, or the heel of an infant when only a small quantity of blood is required. An arterial stick is collected from an artery and used to analyze blood gases. After collection, the blood may be analyzed by medical laboratories or perhaps used for transfusions, donations, or research. While many allied health professionals practice phlebotomy, the American Society of Phlebotomy Technicians issues certificates to individuals passing a national examination, and some large labs and hospitals hire individuals expressly for their skill in phlebotomy.

Medical or clinical laboratories employ a variety of individuals in technical positions:

- Medical technologists (MT), also known as clinical laboratory technologists (CLT), typically hold a bachelor’s degree and certification from an accredited training program. They perform a wide variety of tests on various body fluids, including blood. The information they provide is essential to the primary care providers in determining a diagnosis and in monitoring the course of a disease and response to treatment.
- Medical laboratory technicians (MLT) typically have an associate’s degree but may perform duties similar to those of an MT.
- Medical laboratory assistants (MLA) spend the majority of their time processing samples and carrying out routine assignments within the lab. Clinical training is required, but a degree may not be essential to obtaining a position.

Chapter Review

Blood is a fluid connective tissue critical to the transportation of nutrients, gases, and wastes throughout the body; to defend the body against infection and other threats; and to the homeostatic regulation of pH, temperature, and other internal conditions. Blood is composed of formed elements—erythrocytes, leukocytes, and cell fragments called platelets—and a fluid extracellular matrix called plasma. More than 90 percent of plasma is water. The remainder is mostly plasma proteins—mainly albumin, globulins, and fibrinogen—and other dissolved solutes such as glucose, lipids, electrolytes, and dissolved gases. Because of the formed elements and the plasma proteins and other solutes, blood is sticky and more viscous than water. It is also slightly alkaline, and its temperature is slightly higher than normal body temperature.

Critical Thinking Questions

A patient’s hematocrit is 42 percent. Approximately what percentage of the patient’s blood is plasma?
Why would it be incorrect to refer to the formed elements as cells?
True or false: The buffy coat is the portion of a blood sample that is made up of its proteins.

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Erythrocytes

Learning Objectives

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

- Describe the anatomy of erythrocytes
- Discuss the various steps in the lifecycle of an erythrocyte
- Explain the composition and function of hemoglobin

The erythrocyte, commonly known as a red blood cell (or RBC), is by far the most common formed element: A single drop of blood contains millions of erythrocytes and just thousands of leukocytes. Specifically, males have about 5.4 million erythrocytes per microliter (µL) of blood, and females have approximately 4.8 million per µL. In fact, erythrocytes are estimated to make up about 25 percent of the total cells in the body. As you can imagine, they are quite small cells, with a mean diameter of only about 7–8 micrometers (µm) (Figure 1). The primary functions of erythrocytes are to pick up inhaled oxygen from the lungs and transport it to the body’s tissues, and to pick up some (about 24 percent) carbon dioxide waste at the tissues and transport it to the lungs for exhalation. Erythrocytes remain within the vascular network. Although leukocytes typically leave the blood vessels to perform their defensive functions, movement of erythrocytes from the blood vessels is abnormal.
<table>
<thead>
<tr>
<th>Formed Element</th>
<th>Major Subtypes</th>
<th>Numbers Present per Microliter (μL) and Mean (Range)</th>
<th>Appearance in a Standard Blood Smear</th>
<th>Summary of Functions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes (red blood cells)</td>
<td></td>
<td>5.2 million (4.4–6.0 million)</td>
<td>Flattened biconcave disk; no nucleus; pale red color</td>
<td>Transport oxygen and some carbon dioxide between tissues and lungs</td>
<td>Lifespan of approximately 120 days</td>
</tr>
<tr>
<td>Leukocytes (white blood cells)</td>
<td></td>
<td>7000 (5000–10,000)</td>
<td>Obvious dark-staining nucleus</td>
<td>All function in body defenses</td>
<td>Exit capillaries and move into tissues; lifespan of usually a few hours or days</td>
</tr>
<tr>
<td>Granulocytes including neutrophils, eosinophils, and basophils</td>
<td></td>
<td>4360 (1800–9950)</td>
<td>Abundant granules in cytoplasm; nucleus normally lobed</td>
<td>Nonspecific (innate) resistance to disease</td>
<td>Classified according to membrane-bound granules in cytoplasm</td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td>4150 (1800–7300)</td>
<td>Nuclear lobes increase with age; pale lilac granules</td>
<td>Phagocytic; particularly effective against bacteria. Release cytotoxic chemicals from granules</td>
<td>Most common leukocyte; lifespan of minutes to days</td>
</tr>
<tr>
<td>Eosinophils</td>
<td></td>
<td>165 (0–700)</td>
<td>Nucleus generally two-lobed; bright red-orange granules</td>
<td>Phagocytic cells; particularly effective with antigen-antibody complexes. Release antihistamines. Increase in allergies and parasitic infections</td>
<td>Lifespan of minutes to days</td>
</tr>
<tr>
<td>Basophils</td>
<td></td>
<td>44 (0–150)</td>
<td>Nucleus generally two-lobed but difficult to see due to presence of heavy, dense, dark purple granules</td>
<td>Promotes inflammation</td>
<td>Least common leukocyte; lifespan unknown</td>
</tr>
<tr>
<td>Agranulocytes including lymphocytes and monocytes</td>
<td></td>
<td>2640 (1700–4950)</td>
<td>Lack abundant granules in cytoplasm; have a simple-shaped nucleus that may be indented</td>
<td>Body defenses</td>
<td>Group consists of two major cell types from different lineages</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td></td>
<td>2185 (1500–4000)</td>
<td>Spherical cells with a single often large nucleus occupying much of the cell’s volume; stains purple; seen in large (natural killer cells) and small (B and T cells) variants</td>
<td>Primarily specific (adaptive) immunity: T cells directly attack other cells (cellular immunity). B cells release antibodies (humoral immunity); natural killer cells are similar to T cells but nonspecific</td>
<td>Initial cells originate in bone marrow, but secondary production occurs in lymphatic tissue; several distinct subtypes; memory cells form after exposure to a pathogen and rapidly increase responses to subsequent exposure; lifespan of many years</td>
</tr>
<tr>
<td>Monocytes</td>
<td></td>
<td>455 (200–950)</td>
<td>Largest leukocyte with an indented or horseshoe-shaped nucleus</td>
<td>Very effective phagocytic cells engulfing pathogens or worn out cells; also serve as antigen-presenting cells (APCs) for other components of the immune system</td>
<td>Produced in red bone marrow; referred to as macrophages after leaving circulation</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td>350,000 (150,000–500,000)</td>
<td>Cellular fragments surrounded by a plasma membrane and containing granules; purple stain</td>
<td>Hemostasis plus release growth factors for repair and healing of tissue</td>
<td>Formed from megakaryocytes that remain in the red bone marrow and shed platelets into circulation</td>
</tr>
</tbody>
</table>

*Figure 1. Summary of Formed Elements in Blood*
Shape and Structure of Erythrocytes

As an erythrocyte matures in the red bone marrow, it extrudes its nucleus and most of its other organelles. During the first day or two that it is in the circulation, an immature erythrocyte, known as a reticulocyte, will still typically contain remnants of organelles. Reticulocytes should comprise approximately 1–2 percent of the erythrocyte count and provide a rough estimate of the rate of RBC production, with abnormally low or high rates indicating deviations in the production of these cells. These remnants, primarily of networks (reticulum) of ribosomes, are quickly shed, however, and mature, circulating erythrocytes have few internal cellular structural components. Lacking mitochondria, for example, they rely on anaerobic respiration. This means that they do not utilize any of the oxygen they are transporting, so they can deliver it all to the tissues. They also lack endoplasmic reticula and do not synthesize proteins. Erythrocytes do, however, contain some structural proteins that help the blood cells maintain their unique structure and enable them to change their shape to squeeze through capillaries. This includes the protein spectrin, a cytoskeletal protein element.

Erythrocytes are biconcave disks; that is, they are plump at their periphery and very thin in the center (Figure 2). Since they lack most organelles, there is more interior space for the presence of the hemoglobin molecules that, as you will see shortly, transport gases. The biconcave shape also provides a greater surface area across which gas exchange can occur, relative to its volume; a sphere of a similar diameter would have a lower surface area-to-volume ratio. In the capillaries, the oxygen carried by the erythrocytes can diffuse into the plasma and then through the capillary walls to reach the cells, whereas some of the carbon dioxide produced by the cells as a waste product diffuses into the capillaries to be picked up by the erythrocytes. Capillary beds are extremely narrow, slowing the passage of the erythrocytes and providing an extended opportunity for gas exchange to occur. However, the space within capillaries can be so minute that, despite their own small size, erythrocytes may have to fold in on themselves if they are to make their way through. Fortunately, their structural proteins like spectrin are flexible, allowing them to bend over themselves to a surprising degree, then spring back again when they enter a wider vessel. In wider vessels, erythrocytes may stack up much like a roll of coins, forming a rouleaux, from the French word for “roll.”

Hemoglobin

Hemoglobin is a large molecule made up of proteins and iron. It consists of four folded chains of a protein called globin, designated alpha 1 and 2, and beta 1 and 2 (Figure 3a). Each of these globin molecules is bound to a red pigment molecule called heme, which contains an ion of iron (Fe²⁺) (Figure 3b).
Anatomy

Figure 3. (a) A molecule of hemoglobin contains four globin proteins, each of which is bound to one molecule of the iron-containing pigment heme. (b) A single erythrocyte can contain 300 million hemoglobin molecules, and thus more than 1 billion oxygen molecules.

Each iron ion in the heme can bind to one oxygen molecule; therefore, each hemoglobin molecule can transport four oxygen molecules. An individual erythrocyte may contain about 300 million hemoglobin molecules, and therefore can bind to and transport up to 1.2 billion oxygen molecules (see Figure 3b).

In the lungs, hemoglobin picks up oxygen, which binds to the iron ions, forming oxyhemoglobin. The bright red, oxygenated hemoglobin travels to the body tissues, where it releases some of the oxygen molecules, becoming darker red deoxyhemoglobin, sometimes referred to as reduced hemoglobin. Oxygen release depends on the need for oxygen in the surrounding tissues, so hemoglobin rarely if ever leaves all of its oxygen behind. In the capillaries, carbon dioxide enters the bloodstream. About 76 percent dissolves in the plasma, some of it remaining as dissolved CO₂, and the remainder forming bicarbonate ion. About 23–24 percent of it binds to the amino acids in hemoglobin, forming a molecule known as carbaminohemoglobin. From the capillaries, the hemoglobin carries carbon dioxide back to the lungs, where it releases it for exchange of oxygen.

Changes in the levels of RBCs can have significant effects on the body’s ability to effectively deliver oxygen to the tissues. Ineffective hematopoiesis results in insufficient numbers of RBCs and results in one of several forms of anemia. An overproduction of RBCs produces a condition called polycythemia. The primary drawback with polycythemia is not a failure to directly deliver enough oxygen to the tissues, but rather the increased viscosity of the blood, which makes it more difficult for the heart to circulate the blood.

In patients with insufficient hemoglobin, the tissues may not receive sufficient oxygen, resulting in another form of anemia. In determining oxygenation of tissues, the value of greatest interest in healthcare is the percent saturation; that is, the percentage of hemoglobin sites occupied by oxygen in a patient’s blood. Clinically this value is commonly referred to simply as “percent sat.”

Percent saturation is normally monitored using a device known as a pulse oximeter, which is applied to a thin part of the body, typically the tip of the patient’s finger. The device works by sending two different wavelengths of light (one red, the other infrared) through the finger and measuring the light with a photodetector as it exits. Hemoglobin absorbs light differentially depending upon its saturation with oxygen. The machine calibrates the amount of light received by the photodetector against the amount absorbed by the partially oxygenated hemoglobin and presents the data as percent saturation. Normal pulse oximeter readings range from 95–100 percent. Lower percentages reflect hypoxemia, or low blood oxygen. The term hypoxia is more generic and simply refers to low oxygen levels. Oxygen levels are also directly monitored from free oxygen in the plasma typically following an arterial stick. When this method is applied, the amount of oxygen present is expressed in terms of partial pressure of oxygen or simply pO₂ and is typically recorded in units of millimeters of mercury, mm Hg.

The kidneys filter about 180 liters (~380 pints) of blood in an average adult each day, or about 20 percent of the total resting volume, and thus serve as ideal sites for receptors that determine oxygen saturation. In response to hypoxemia, less oxygen will exit the vessels supplying the kidney, resulting in hypoxia (low oxygen concentration) in the tissue fluid of the kidney where oxygen concentration is actually monitored. Interstitial fibroblasts within
the kidney secrete EPO, thereby increasing erythrocyte production and restoring oxygen levels. In a classic
negative-feedback loop, as oxygen saturation rises, EPO secretion falls, and vice versa, thereby maintaining
homeostasis. Populations dwelling at high elevations, with inherently lower levels of oxygen in the atmosphere,
naturally maintain a hematocrit higher than people living at sea level. Consequently, people traveling to high
elevations may experience symptoms of hypoxemia, such as fatigue, headache, and shortness of breath, for a few
days after their arrival. In response to the hypoxemia, the kidneys secrete EPO to step up the production of
erthrocytes until homeostasis is achieved once again. To avoid the symptoms of hypoxemia, or altitude sickness,
mountain climbers typically rest for several days to a week or more at a series of camps situated at increasing
elevations to allow EPO levels and, consequently, erythrocyte counts to rise. When climbing the tallest peaks, such
as Mt. Everest and K2 in the Himalayas, many mountain climbers rely upon bottled oxygen as they near the
summit.

**Lifecycle of Erythrocytes**

Production of erythrocytes in the marrow occurs at the staggering rate of more than 2 million cells per second.
For this production to occur, a number of raw materials must be present in adequate amounts. These include the
same nutrients that are essential to the production and maintenance of any cell, such as glucose, lipids, and amino
acids. However, erythrocyte production also requires several trace elements:

- **Iron.** We have said that each heme group in a hemoglobin molecule contains an ion of the trace
  mineral iron. On average, less than 20 percent of the iron we consume is absorbed. Heme iron,
  from animal foods such as meat, poultry, and fish, is absorbed more efficiently than non-heme iron
  from plant foods. Upon absorption, iron becomes part of the body's total iron pool. The bone
  marrow, liver, and spleen can store iron in the protein compounds **ferritin** and **hemosiderin**.
  Ferroportin transports the iron across the intestinal cell plasma membranes and from its storage
  sites into tissue fluid where it enters the blood. When EPO stimulates the production of
  erythrocytes, iron is released from storage, bound to transferrin, and carried to the red marrow
  where it attaches to erythrocyte precursors.

- **Copper.** A trace mineral, copper is a component of two plasma proteins, hephaestin and
ceruloplasmin. Without these, hemoglobin could not be adequately produced. Located in intestinal
villi, hephaestin enables iron to be absorbed by intestinal cells. Ceruloplasmin transports copper.
Both enable the oxidation of iron from Fe$_{2+}$ to Fe$_{3+}$, a form in which it can be bound to its
transport protein, **transferrin**, for transport to body cells. In a state of copper deficiency, the
transport of iron for heme synthesis decreases, and iron can accumulate in tissues, where it can
eventually lead to organ damage.

- **Zinc.** The trace mineral zinc functions as a co-enzyme that facilitates the synthesis of the heme
  portion of hemoglobin.

- **B vitamins.** The B vitamins folate and vitamin B$_{12}$ function as co-enzymes that facilitate DNA
  synthesis. Thus, both are critical for the synthesis of new cells, including erythrocytes.

Erythrocytes live up to 120 days in the circulation, after which the worn-out cells are removed by a type of
myeloid phagocytic cell called a **macrophage**, located primarily within the bone marrow, liver, and spleen. The
components of the degraded erythrocytes’ hemoglobin are further processed as follows:

- **Globin,** the protein portion of hemoglobin, is broken down into amino acids, which can be sent
  back to the bone marrow to be used in the production of new erythrocytes. Hemoglobin that is not
  phagocytized is broken down in the circulation, releasing alpha and beta chains that are removed
  from circulation by the kidneys.

- The iron contained in the heme portion of hemoglobin may be stored in the liver or spleen,
  primarily in the form of ferritin or hemosiderin, or carried through the bloodstream by transferrin
to the red bone marrow for recycling into new erythrocytes.

- The non-iron portion of heme is degraded into the waste product **biliverdin,** a green pigment, and
  then into another waste product, **bilirubin,** a yellow pigment. Bilirubin binds to albumin and
  travels in the blood to the liver, which uses it in the manufacture of bile, a compound released
  into the intestines to help emulsify dietary fats. In the large intestine, bacteria breaks the bilirubin
  apart from the bile and converts it to urobilinogen and then into stercobilin. It is then eliminated
  from the body in the feces. Broad-spectrum antibiotics typically eliminate these bacteria as well.
Anatomy

and may alter the color of feces. The kidneys also remove any circulating bilirubin and other related metabolic byproducts such as urobilins and secrete them into the urine. The breakdown pigments formed from the destruction of hemoglobin can be seen in a variety of situations. At the site of an injury, biliverdin from damaged RBCs produces some of the dramatic colors associated with bruising. With a failing liver, bilirubin cannot be removed effectively from circulation and causes the body to assume a yellowish tinge associated with jaundice. Stercobilins within the feces produce the typical brown color associated with this waste. And the yellow of urine is associated with the urobilins. The erythrocyte lifecycle is summarized in Figure 4.

Figure 4. Erythrocytes are produced in the bone marrow and sent into the circulation. At the end of their lifecycle, they are destroyed by macrophages, and their components are recycled.
Disorders of Erythrocytes

The size, shape, and number of erythrocytes, and the number of hemoglobin molecules can have a major impact on a person’s health. When the number of RBCs or hemoglobin is deficient, the general condition is called anemia. There are more than 400 types of anemia and more than 3.5 million Americans suffer from this condition. Anemia can be broken down into three major groups: those caused by blood loss, those caused by faulty or decreased RBC production, and those caused by excessive destruction of RBCs. Clinicians often use two groupings in diagnosis: The kinetic approach focuses on evaluating the production, destruction, and removal of RBCs, whereas the morphological approach examines the RBCs themselves, paying particular emphasis to their size. A common test is the mean corpuscle volume (MCV), which measures size. Normal-sized cells are referred to as normocytic, smaller-than-normal cells are referred to as microcytic, and larger-than-normal cells are referred to as macrocytic. Reticulocyte counts are also important and may reveal inadequate production of RBCs. The effects of the various anemias are widespread, because reduced numbers of RBCs or hemoglobin will result in lower levels of oxygen being delivered to body tissues. Since oxygen is required for tissue functioning, anemia produces fatigue, lethargy, and an increased risk for infection. An oxygen deficit in the brain impairs the ability to think clearly, and may prompt headaches and irritability. Lack of oxygen leaves the patient short of breath, even as the heart and lungs work harder in response to the deficit.

Blood loss anemias are fairly straightforward. In addition to bleeding from wounds or other lesions, these forms of anemia may be due to ulcers, hemorrhoids, inflammation of the stomach (gastritis), and some cancers of the gastrointestinal tract. The excessive use of aspirin or other nonsteroidal anti-inflammatory drugs such as ibuprofen can trigger ulceration and gastritis. Excessive menstruation and loss of blood during childbirth are also potential causes.

Anemias caused by faulty or decreased RBC production include sickle cell anemia, iron deficiency anemia, vitamin deficiency anemia, and diseases of the bone marrow and stem cells.

- A characteristic change in the shape of erythrocytes is seen in sickle cell disease (also referred to as sickle cell anemia). A genetic disorder, it is caused by production of an abnormal type of hemoglobin, called hemoglobin S, which delivers less oxygen to tissues and causes erythrocytes to assume a sickle (or crescent) shape, especially at low oxygen concentrations (Figure 5). These abnormally shaped cells can then become lodged in narrow capillaries because they are unable to fold in on themselves to squeeze through, blocking blood flow to tissues and causing a variety of serious problems from painful joints to delayed growth and even blindness and cerebrovascular accidents (strokes). Sickle cell anemia is a genetic condition particularly found in individuals of African descent.

- Iron deficiency anemia is the most common type and results when the amount of available iron is insufficient to allow production of sufficient heme. This condition can occur in individuals with a deficiency of iron in the diet and is especially common in teens and children as well as in vegans and vegetarians. Additionally, iron deficiency anemia may be caused by either an inability to absorb and transport iron or slow, chronic bleeding.

- Vitamin-deficient anemias generally involve insufficient vitamin B12 and folate.
  - Megaloblastic anemia involves a deficiency of vitamin B12 and/or folate, and often involves diets deficient in these essential nutrients.
Lack of meat or a viable alternate source, and overcooking or eating insufficient amounts of vegetables may lead to a lack of folate. Pernicious anemia is caused by poor absorption of vitamin B12 and is often seen in patients with Crohn’s disease (a severe intestinal disorder often treated by surgery), surgical removal of the intestines or stomach (common in some weight loss surgeries), intestinal parasites, and AIDS. Pregnancies, some medications, excessive alcohol consumption, and some diseases such as celiac disease are also associated with vitamin deficiencies. It is essential to provide sufficient folic acid during the early stages of pregnancy to reduce the risk of neurological defects, including spina bifida, a failure of the neural tube to close.

- Assorted disease processes can also interfere with the production and formation of RBCs and hemoglobin. If myeloid stem cells are defective or replaced by cancer cells, there will be insufficient quantities of RBCs produced.

  - Aplastic anemia is the condition in which there are deficient numbers of RBC stem cells. Aplastic anemia is often inherited, or it may be triggered by radiation, medication, chemotherapy, or infection. **Thalassemia** is an inherited condition typically occurring in individuals from the Middle East, the Mediterranean, African, and Southeast Asia, in which maturation of the RBCs does not proceed normally. The most severe form is called Cooley’s anemia. Lead exposure from industrial sources or even dust from paint chips of iron-containing paints or pottery that has not been properly glazed may also lead to destruction of the red marrow.

- Various disease processes also can lead to anemias. These include chronic kidney diseases often associated with a decreased production of EPO, hypothyroidism, some forms of cancer, lupus, and rheumatoid arthritis.

In contrast to anemia, an elevated RBC count is called **polycythemia** and is detected in a patient’s elevated hematocrit. It can occur transiently in a person who is dehydrated; when water intake is inadequate or water losses are excessive, the plasma volume falls. As a result, the hematocrit rises. For reasons mentioned earlier, a mild form of polycythemia is chronic but normal in people living at high altitudes. Some elite athletes train at high elevations specifically to induce this phenomenon. Finally, a type of bone marrow disease called polycythemia vera (from the Greek *vera* = “true”) causes an excessive production of immature erythrocytes. Polycythemia vera can dangerously elevate the viscosity of blood, raising blood pressure and making it more difficult for the heart to pump blood throughout the body. It is a relatively rare disease that occurs more often in men than women, and is more likely to be present in elderly patients those over 60 years of age.
Chapter Review

The most abundant formed elements in blood, erythrocytes are red, biconcave disks packed with an oxygen-carrying compound called hemoglobin. The hemoglobin molecule contains four globin proteins bound to a pigment molecule called heme, which contains an ion of iron. In the bloodstream, iron picks up oxygen in the lungs and drops it off in the tissues; the amino acids in hemoglobin then transport carbon dioxide from the tissues back to the lungs.

Erythrocytes live only 120 days on average, and thus must be continually replaced. Worn-out erythrocytes are phagocytized by macrophages and their hemoglobin is broken down. The breakdown products are recycled or removed as wastes: Globin is broken down into amino acids for synthesis of new proteins; iron is stored in the liver or spleen or used by the bone marrow for production of new erythrocytes; and the remnants of heme are converted into bilirubin, or other waste products that are taken up by the liver and excreted in the bile or removed by the kidneys. Anemia is a deficiency of RBCs or hemoglobin, whereas polycythemia is an excess of RBCs.

Critical Thinking Questions

- young woman has been experiencing unusually heavy menstrual bleeding for several years. She follows a strict vegan diet (no animal foods). She is at risk for what disorder, and why?
- A patient has thalassemia, a genetic disorder characterized by abnormal synthesis of globin proteins and excessive destruction of erythrocytes. This patient is jaundiced and is found to have an excessive level of bilirubin in his blood. Explain the connection.

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Leukocytes and Platelets

Learning Objectives

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

- Describe the general characteristics of leukocytes
- Classify leukocytes according to their lineage, their main structural features, and their primary functions
- Discuss the most common malignancies involving leukocytes
- Identify the lineage, basic structure, and function of platelets

The leukocyte, commonly known as a white blood cell (or WBC), is a major component of the body’s defenses against disease. Leukocytes protect the body against invading microorganisms and body cells with mutated DNA, and they clean up debris. Platelets are essential for the repair of blood vessels when damage to them has occurred; they also provide growth factors for healing and repair. See Figure 1 in Erythrocytes for a summary of leukocytes and platelets.

Characteristics of Leukocytes

Although leukocytes and erythrocytes both originate from hematopoietic stem cells in the bone marrow, they are very different from each other in many significant ways. For instance, leukocytes are far less numerous than erythrocytes: typically there are only 5000 to 10,000 per μL. They are also larger than erythrocytes and are the only formed elements that are complete cells, possessing a nucleus and organelles. And although there is just one type of erythrocyte, there are many types of leukocytes. Most of these types have a much shorter lifespan than that of erythrocytes, some as short as a few hours or even a few minutes in the case of acute infection.

One of the most distinctive characteristics of leukocytes is their movement. Whereas erythrocytes spend their days circulating within the blood vessels, leukocytes routinely leave the bloodstream to perform their defensive functions in the body’s tissues. For leukocytes, the vascular network is simply a highway they travel and soon exit to reach their true destination. When they arrive, they are often given distinct names, such as macrophage or microglia, depending on their function. As shown in Figure 1, they leave the capillaries—the smallest blood vessels—or other small vessels through a process known as emigration (from the Latin for “removal”) or diapedesis (dia- = “through”; -pedan = “to leap”) in which they squeeze through adjacent cells in a blood vessel wall.
Figure 1. **Leukocytes exit the blood vessel and then move through the connective tissue of the dermis toward the site of a wound.** Some leukocytes, such as the eosinophil and neutrophil, are characterized as granular leukocytes. They release chemicals from their granules that destroy pathogens; they are also capable of phagocytosis. The monocyte, an agranular leukocyte, differentiates into a macrophage that then phagocytizes the pathogens.

Once they have exited the capillaries, some leukocytes will take up fixed positions in lymphatic tissue, bone marrow, the spleen, the thymus, or other organs. Others will move about through the tissue spaces very much like amoebas, continuously extending their plasma membranes, sometimes wandering freely, and sometimes moving toward the direction in which they are drawn by chemical signals. This attracting of leukocytes occurs because of **positive chemotaxis** (literally “movement in response to chemicals”), a phenomenon in which injured or infected cells and nearby leukocytes emit the equivalent of a chemical “911” call, attracting more leukocytes to the site. In clinical medicine, the differential counts of the types and percentages of leukocytes present are often key indicators in making a diagnosis and selecting a treatment.

### Classification of Leukocytes

When scientists first began to observe stained blood slides, it quickly became evident that leukocytes could be divided into two groups, according to whether their cytoplasm contained highly visible granules:

- **Granular leukocytes** contain abundant granules within the cytoplasm. They include neutrophils, eosinophils, and basophils (you can view their lineage from myeloid stem cells in Figure 1 in Production of the Formed Elements).
- While granules are not totally lacking in **agranular leukocytes**, they are far fewer and less obvious. Agranular leukocytes include monocytes, which mature into macrophages that are phagocytic, and lymphocytes, which arise from the lymphoid stem cell line.

### Granular Leukocytes

We will consider the granular leukocytes in order from most common to least common. All of these are produced in the red bone marrow and have a short lifespan of hours to days. They typically have a lobed nucleus and are classified according to which type of stain best highlights their granules (Figure 2).
Figure 2. A neutrophil has small granules that stain light lilac and a nucleus with two to five lobes. An eosinophil’s granules are slightly larger and stain reddish-orange, and its nucleus has two to three lobes. A basophil has large granules that stain dark blue to purple and a two-lobed nucleus.

The most common of all the leukocytes, neutrophils will normally comprise 50–70 percent of total leukocyte count. They are 10–12 µm in diameter, significantly larger than erythrocytes. They are called neutrophils because their granules show up most clearly with stains that are chemically neutral (neither acidic nor basic). The granules are numerous but quite fine and normally appear light lilac. The nucleus has a distinct lobed appearance and may have two to five lobes, the number increasing with the age of the cell. Older neutrophils have increasing numbers of lobes and are often referred to as polymorphonuclear (a nucleus with many forms), or simply “polys.” Younger and immature neutrophils begin to develop lobes and are known as “bands.”

Neutrophils are rapid responders to the site of infection and are efficient phagocytes with a preference for bacteria. Their granules include lysozyme, an enzyme capable of lysing, or breaking down, bacterial cell walls; oxidants such as hydrogen peroxide; and defensins, proteins that bind to and puncture bacterial and fungal plasma membranes, so that the cell contents leak out. Abnormally high counts of neutrophils indicate infection and/or inflammation, particularly triggered by bacteria, but are also found in burn patients and others experiencing unusual stress. A burn injury increases the proliferation of neutrophils in order to fight off infection that can result from the destruction of the barrier of the skin. Low counts may be caused by drug toxicity and other disorders, and may increase an individual’s susceptibility to infection.

Eosinophils typically represent 2–4 percent of total leukocyte count. They are also 10–12 µm in diameter. The granules of eosinophils stain best with an acidic stain known as eosin. The nucleus of the eosinophil will typically have two to three lobes and, if stained properly, the granules will have a distinct red to orange color.

The granules of eosinophils include antihistamine molecules, which counteract the activities of histamines, inflammatory chemicals produced by basophils and mast cells. Some eosinophil granules contain molecules toxic to parasitic worms, which can enter the body through the integument, or when an individual consumes raw or undercooked fish or meat. Eosinophils are also capable of phagocytosis and are particularly effective when antibodies bind to the target and form an antigen-antibody complex. High counts of eosinophils are typical of patients experiencing allergies, parasitic worm infestations, and some autoimmune diseases. Low counts may be due to drug toxicity and stress.

Basophils are the least common leukocytes, typically comprising less than one percent of the total leukocyte count. They are slightly smaller than neutrophils and eosinophils at 8–10 µm in diameter. The granules of basophils stain best with basic (alkaline) stains. Basophils contain large granules that pick up a dark blue stain and are so common they may make it difficult to see the two-lobed nucleus.

In general, basophils intensify the inflammatory response. They share this trait with mast cells. In the past, mast cells were considered to be basophils that left the circulation. However, this appears not to be the case, as the two cell types develop from different lineages.

The granules of basophils release histamines, which contribute to inflammation, and heparin, which opposes blood clotting. High counts of basophils are associated with allergies, parasitic infections, and hypothyroidism. Low counts are associated with pregnancy, stress, and hyperthyroidism.
Agranulocytes contain smaller, less-visible granules in their cytoplasm than do granular leukocytes. The nucleus is simple in shape, sometimes with an indentation but without distinct lobes. There are two major types of agranulocytes: lymphocytes and monocytes (see Figure 1 in Production of the Formed Elements).

**Lymphocytes** are the only formed element of blood that arises from lymphoid stem cells. Although they form initially in the bone marrow, much of their subsequent development and reproduction occurs in the lymphatic tissues. Lymphocytes are the second most common type of leukocyte, accounting for about 20–30 percent of all leukocytes, and are essential for the immune response. The size range of lymphocytes is quite extensive, with some authorities recognizing two size classes and others three. Typically, the large cells are 10–14 \( \mu \text{m} \) and have a smaller nucleus-to-cytoplasm ratio and more granules. The smaller cells are typically 6–9 \( \mu \text{m} \) with a larger volume of nucleus to cytoplasm, creating a “halo” effect. A few cells may fall outside these ranges, at 14–17 \( \mu \text{m} \). This finding has led to the three size range classification.

The three major groups of lymphocytes include natural killer cells, B cells, and T cells. **Natural killer (NK) cells** are capable of recognizing cells that do not express “self” proteins on their plasma membrane or that contain foreign or abnormal markers. These “nonself” cells include cancer cells, cells infected with a virus, and other cells with atypical surface proteins. Thus, they provide generalized, nonspecific immunity. The larger lymphocytes are typically NK cells.

B cells and T cells, also called **B lymphocytes** and **T lymphocytes**, play prominent roles in defending the body against specific pathogens (disease-causing microorganisms) and are involved in specific immunity. One form of B cells (plasma cells) produces the antibodies or immunoglobulins that bind to specific foreign or abnormal components of plasma membranes. This is also referred to as humoral (body fluid) immunity. **T cells** provide cellular-level immunity by physically attacking foreign or diseased cells. A **memory cell** is a variety of both B and T cells that forms after exposure to a pathogen and mounts rapid responses upon subsequent exposures. Unlike other leukocytes, memory cells live for many years. B cells undergo a maturation process in the bone marrow, whereas T cells undergo maturation in the thymus. This site of the maturation process gives rise to the name B and T cells. The functions of lymphocytes are complex and will be covered in detail in the chapter covering the lymphatic system and immunity. Smaller lymphocytes are either B or T cells, although they cannot be differentiated in a normal blood smear.

Abnormally high lymphocyte counts are characteristic of viral infections as well as some types of cancer. Abnormally low lymphocyte counts are characteristic of prolonged (chronic) illness or immunosuppression, including that caused by HIV infection and drug therapies that often involve steroids.

**Monocytes** originate from myeloid stem cells. They normally represent 2–8 percent of the total leukocyte count. They are typically easily recognized by their large size of 12–20 \( \mu \text{m} \) and indented or horseshoe-shaped nuclei. Macrophages are monocytes that have left the circulation and phagocytize debris, foreign pathogens, worn-out erythrocytes, and many other dead, worn out, or damaged cells. Macrophages also release antimicrobial defensins and chemotactic chemicals that attract other leukocytes to the site of an infection. Some macrophages occupy fixed locations, whereas others wander through the tissue fluid.

Abnormally high counts of monocytes are associated with viral or fungal infections, tuberculosis, and some forms of leukemia and other chronic diseases. Abnormally low counts are typically caused by suppression of the bone marrow.

**Lifecycle of Leukocytes**

Most leukocytes have a relatively short lifespan, typically measured in hours or days. Production of all leukocytes begins in the bone marrow under the influence of CSFs and interleukins. Secondary production and maturation of lymphocytes occurs in specific regions of lymphatic tissue known as germinal centers. Lymphocytes are fully capable of mitosis and may produce clones of cells with identical properties. This capacity enables an individual to maintain immunity throughout life to many threats that have been encountered in the past.
Disorders of Leukocytes

**Leukopenia** is a condition in which too few leukocytes are produced. If this condition is pronounced, the individual may be unable to ward off disease. Excessive leukocyte proliferation is known as **leukocytosis**. Although leukocyte counts are high, the cells themselves are often nonfunctional, leaving the individual at increased risk for disease.

**Leukemia** is a cancer involving an abundance of leukocytes. It may involve only one specific type of leukocyte from either the myeloid line (myelocytic leukemia) or the lymphoid line (lymphocytic leukemia). In chronic leukemia, mature leukocytes accumulate and fail to die. In acute leukemia, there is an overproduction of young, immature leukocytes. In both conditions the cells do not function properly.

**Lymphoma** is a form of cancer in which masses of malignant T and/or B lymphocytes collect in lymph nodes, the spleen, the liver, and other tissues. As in leukemia, the malignant leukocytes do not function properly, and the patient is vulnerable to infection. Some forms of lymphoma tend to progress slowly and respond well to treatment. Others tend to progress quickly and require aggressive treatment, without which they are rapidly fatal.

Platelets

You may occasionally see platelets referred to as **thrombocytes**, but because this name suggests they are a type of cell, it is not accurate. A platelet is not a cell but rather a fragment of the cytoplasm of a cell called a **megakaryocyte** that is surrounded by a plasma membrane. Megakaryocytes are descended from myeloid stem cells (see Figure 1 in Production of the Formed Elements) and are large, typically 50–100 µm in diameter, and contain an enlarged, lobed nucleus. As noted earlier, thrombopoietin, a glycoprotein secreted by the kidneys and liver, stimulates the proliferation of megakaryoblasts, which mature into megakaryocytes.
Platelets are derived from cells called megakaryocytes. These remain within bone marrow tissue (Figure 3) and ultimately form platelet-precursor extensions that extend through the walls of bone marrow capillaries to release into the circulation thousands of cytoplasmic fragments, each enclosed by a bit of plasma membrane. These enclosed fragments are platelets. Each megakaryocyte releases 2000–3000 platelets during its lifespan. Following platelet release, megakaryocyte remnants, which are little more than a cell nucleus, are consumed by macrophages.

Platelets are relatively small, 2–4 µm in diameter, but numerous, with typically 150,000–160,000 per µL of blood. After entering the circulation, approximately one-third migrate to the spleen for storage for later release in response to any rupture in a blood vessel. They then become activated to perform their primary function, which is to limit blood loss. Platelets remain only about 10 days, then are phagocytized by macrophages.

Platelets are critical to hemostasis, the stoppage of blood flow following damage to a vessel. They also secrete a variety of growth factors essential for growth and repair of tissue, particularly connective tissue. Infusions of concentrated platelets are now being used in some therapies to stimulate healing.

Disorders of Platelets

Thrombocytosis is a condition in which there are too many platelets. This may trigger formation of unwanted blood clots (thrombosis), a potentially fatal disorder. If there is an insufficient number of platelets, called thrombocytopenia, blood may not clot properly, and excessive bleeding may result.
Practice Question

View University of Michigan Webscopes (link in online textbook) and explore the blood slides in greater detail. The Webscope feature allows you to move the slides as you would with a mechanical stage. You can increase and decrease the magnification. There is a chance to review each of the leukocytes individually after you have attempted to identify them from the first two blood smears. In addition, there are a few multiple choice questions. Are you able to recognize and identify the various formed elements? You will need to do this is a systematic manner, scanning along the image. The standard method is to use a grid, but this is not possible with this resource. Try constructing a simple table with each leukocyte type and then making a mark for each cell type you identify. Attempt to classify at least 50 and perhaps as many as 100 different cells. Based on the percentage of cells that you count, do the numbers represent a normal blood smear or does something appear to be abnormal?

Chapter Review

Leukocytes function in body defenses. They squeeze out of the walls of blood vessels through emigration or diapedesis, then may move through tissue fluid or become attached to various organs where they fight against pathogenic organisms, diseased cells, or other threats to health. Granular leukocytes, which include neutrophils, eosinophils, and basophils, originate with myeloid stem cells, as do the agranular monocytes. The other agranular leukocytes, NK cells, B cells, and T cells, arise from the lymphoid stem cell line. The most abundant leukocytes are the neutrophils, which are first responders to infections, especially with bacteria. About 20–30 percent of all leukocytes are lymphocytes, which are critical to the body’s defense against specific threats. Leukemia and lymphoma are malignancies involving leukocytes. Platelets are fragments of cells known as megakaryocytes that dwell within the bone marrow. While many platelets are stored in the spleen, others enter the circulation and are essential for hemostasis; they also produce several growth factors important for repair and healing.

Critical Thinking Questions

One of the more common adverse effects of cancer chemotherapy is the destruction of leukocytes. Before his next scheduled chemotherapy treatment, a patient undergoes a blood test called an absolute neutrophil count (ANC), which reveals that his neutrophil count is 1900 cells per microliter. Would his healthcare team be likely to proceed with his chemotherapy treatment? Why?

A patient was admitted to the burn unit the previous evening suffering from a severe burn involving his left upper extremity and shoulder. A blood test reveals that he is experiencing leukocytosis. Why is this an expected finding?

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Blood Typing

Learning Objectives

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

- Describe the two basic physiological consequences of transfusion of incompatible blood
- 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

Blood transfusions in humans were risky procedures until the discovery of the major human blood groups by Karl Landsteiner, an Austrian biologist and physician, in 1900. Until that point, physicians did not understand that death sometimes followed blood transfusions, when the type of donor blood infused into the patient was incompatible with the patient’s own blood. Blood groups are determined by the presence or absence of specific marker molecules on the plasma membranes of erythrocytes. With their discovery, it became possible for the first time to match patient-donor blood types and prevent transfusion reactions and deaths.

Antigens, Antibodies, and Transfusion Reactions

Antigens are substances that the body does not recognize as belonging to the “self” and that therefore trigger a defensive response from the leukocytes of the immune system. (Seek more content for additional information on immunity.) Here, we will focus on the role of immunity in blood transfusion reactions. With RBCs in particular, you may see the antigens referred to as isoantigens or agglutinogens (surface antigens) and the antibodies referred to as isoantibodies or agglutinins. In this chapter, we will use the more common terms antigens and antibodies.

Antigens are generally large proteins, but may include other classes of organic molecules, including carbohydrates, lipids, and nucleic acids. Following an infusion of incompatible blood, erythrocytes with foreign antigens appear in the bloodstream and trigger an immune response. Proteins called antibodies (immunoglobulins), which are produced by certain B lymphocytes called plasma cells, attach to the antigens on the plasma membranes of the infused erythrocytes and cause them to adhere to one another.

- Because the arms of the Y-shaped antibodies attach randomly to more than one nonself erythrocyte surface, they form clumps of erythrocytes. This process is called agglutination.
- The clumps of erythrocytes block small blood vessels throughout the body, depriving tissues of oxygen and nutrients.
- As the erythrocyte clumps are degraded, in a process called hemolysis, their hemoglobin is released into the bloodstream. This hemoglobin travels to the kidneys, which are responsible for filtration of the blood. However, the load of hemoglobin released can easily overwhelm the kidney’s capacity to clear it, and the patient can quickly develop kidney failure.

More than 50 antigens have been identified on erythrocyte membranes, but the most significant in terms of their potential harm to patients are classified in two groups: the ABO blood group and the Rh blood group.
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.

Normally the body must be exposed to a foreign antigen before an antibody can be produced. This is not the case for the ABO blood group. Individuals with type A blood—without any prior exposure to incompatible blood—have preformed 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 pre-formed anti-A antibodies. Individuals with type AB blood, which has both antigens, do not have preformed 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.

The following chart summarizes the distribution of the ABO and Rh blood types within the United States.

<table>
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<th>Asian-Americans</th>
<th>Caucasian-Americans</th>
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</tr>
<tr>
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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− gestational parent. 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 baby and the parent). 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 gestational parent’s immune system begins to generate anti-Rh antibodies. If the parent should then conceive 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 1. The first exposure of an Rh− gestational parent to Rh+ erythrocytes during pregnancy induces sensitization. Anti-Rh antibodies begin to circulate in the parent's bloodstream. A second exposure occurs with a subsequent pregnancy with an Rh+ fetus in the uterus. Parental 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− gestational 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− mothers 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− gestational parent is about 13–14 percent without preventive treatment. Since the introduction of RhoGAM in 1968, the incidence has dropped to about 0.1 percent in the United States.

Determining ABO Blood Types

Clinicians are able to determine a patient’s blood type quickly and easily using commercially prepared antibodies. An unknown blood sample is allocated into separate wells. Into one well a small amount of anti-A antibody is added, and to another a small amount of anti-B antibody. If the antigen is present, the antibodies will cause visible agglutination of the cells (Figure 2). The blood should also be tested for Rh antibodies.

Figure 2. This sample of a commercially produced “bedside” card enables quick typing of both a recipient’s and donor’s blood before transfusion. The card contains three reaction sites or wells. One is coated with an anti-A antibody, one with an anti-B antibody, and one with an anti-D antibody (tests for the presence of Rh factor D). Mixing a drop of blood and saline into each well enables the blood to interact with a preparation of type-specific antibodies, also called anti-seras. Agglutination of RBCs in a given site indicates a positive identification of the blood antigens, in this case A and Rh antigens for blood type A+. For the purpose of transfusion, the donor’s and recipient’s blood types must match.

ABO Transfusion Protocols

To avoid transfusion reactions, it is best to transfuse only matching blood types; that is, a type B+ recipient should ideally receive blood only from a type B+ donor and so on. That said, in emergency situations, when acute hemorrhage threatens the patient’s life, there may not be time for cross matching to identify blood type. In these cases, blood from a universal donor—an individual with type O− blood—may be transfused. Recall that type O erythrocytes do not display A or B antigens. Thus, anti-A or anti-B antibodies that might be circulating in the patient’s blood plasma will not encounter any erythrocyte surface antigens on the donated blood and therefore will not be provoked into a response. One problem with this designation of universal donor is if the O− individual had prior exposure to Rh antigen, Rh antibodies may be present in the donated blood. Also, introducing type O blood into an individual with type A, B, or AB blood will nevertheless introduce antibodies against both A and B antigens, as these are always circulating in the type O blood plasma. This may cause problems for the recipient, but because the volume of blood transfused is much lower than the volume of the patient’s own blood, the adverse
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effects of the relatively few infused plasma antibodies are typically limited. Rh factor also plays a role. If Rh\(^-\) individuals receiving blood have had prior exposure to Rh antigen, antibodies for this antigen may be present in the blood and trigger agglutination to some degree. Although it is always preferable to cross match a patient’s blood before transfusing, in a true life-threatening emergency situation, this is not always possible, and these procedures may be implemented.

A patient with blood type AB\(^+\) is known as the **universal recipient**. This patient can theoretically receive any type of blood, because the patient’s own blood—having both A and B antigens on the erythrocyte surface—does not produce anti-A or anti-B antibodies. In addition, an Rh\(^+\) patient can receive both Rh\(^+\) and Rh\(^-\) blood. However, keep in mind that the donor’s blood will contain circulating antibodies, again with possible negative implications. Figure 3 summarizes the blood types and compatibilities.

At the scene of multiple-vehicle accidents, military engagements, and natural or human-caused disasters, many victims may suffer simultaneously from acute hemorrhage, yet type O blood may not be immediately available. In these circumstances, medics may at least try to replace some of the volume of blood that has been lost. This is done by intravenous administration of a saline solution that provides fluids and electrolytes in proportions equivalent to those of normal blood plasma. Research is ongoing to develop a safe and effective artificial blood that would carry out the oxygen-carrying function of blood without the RBCs, enabling transfusions in the field without concern for incompatibility. These blood substitutes normally contain hemoglobin- as well as perfluorocarbon-based oxygen carriers.

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### Blood Type

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<td>B, O</td>
<td>A, B, AB, O (AB(^+) is the universal recipient)</td>
<td>O (O is the universal donor)</td>
</tr>
</tbody>
</table>

*Figure 3. This chart summarizes the characteristics of the blood types in the ABO blood group. See the text for more on the concept of a universal donor or recipient.*
Chapter Review

Antigens are nonself molecules, usually large proteins, which provoke an immune response. In transfusion reactions, antibodies attach to antigens on the surfaces of erythrocytes and cause agglutination and hemolysis. ABO blood group antigens are designated A and B. People with type A blood have A antigens on their erythrocytes, whereas those with type B blood have B antigens. Those with AB blood have both A and B antigens, and those with type O blood have neither A nor B antigens. The blood plasma contains preformed antibodies against the antigens not present on a person’s erythrocytes.

A second group of blood antigens is the Rh group, the most important of which is Rh D. People with Rh− blood do not have this antigen on their erythrocytes, whereas those who are Rh+ do. About 85 percent of Americans are Rh+. When a woman who is Rh− becomes pregnant with an Rh+ fetus, her body may begin to produce anti-Rh antibodies. If she subsequently becomes pregnant with a second Rh+ fetus and is not treated preventively with RhoGAM, the fetus will be at risk for an antigen-antibody reaction, including agglutination and hemolysis. This is known as hemolytic disease of the newborn.

Cross matching to determine blood type is necessary before transfusing blood, unless the patient is experiencing hemorrhage that is an immediate threat to life, in which case type O− blood may be transfused.

Critical Thinking Questions

Following a motor vehicle accident, a patient is rushed to the emergency department with multiple traumatic injuries, causing severe bleeding. The patient’s condition is critical, and there is no time for determining his blood type. What type of blood is transfused, and why?

In preparation for a scheduled surgery, a patient visits the hospital lab for a blood draw. The technician collects a blood sample and performs a test to determine its type. She places a sample of the patient’s blood in two wells. To the first well she adds anti-A antibody. To the second she adds anti-B antibody. Both samples visibly agglutinate. Has the technician made an error, or is this a normal response? If normal, what blood type does this indicate?

References


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Section 17: The Cardiovascular System: The Heart
Introduction to the Cardiovascular System:
The Heart

Learning Objectives

After studying this chapter, you will be able to:

- Identify and describe the interior and exterior parts of the human heart
- Describe the path of blood through the cardiac circuits
- Describe the size, shape, and location of the heart
- Compare cardiac muscle to skeletal and smooth muscle
- Explain the cardiac conduction system
- Describe the process and purpose of an electrocardiogram
- Explain the cardiac cycle
- Calculate cardiac output
- Describe the effects of exercise on cardiac output and heart rate
- Name the centers of the brain that control heart rate and describe their function
- Identify other factors affecting heart rate
- Describe fetal heart development

In this chapter, you will explore the remarkable pump that propels the blood into the vessels. There is no single better word to describe the function of the heart other than “pump,” since its contraction develops the pressure that ejects blood into the major vessels: the aorta and pulmonary trunk. From these vessels, the blood is distributed to the remainder of the body. Although the connotation of the term “pump” suggests a mechanical device made of steel and plastic, the anatomical structure is a living, sophisticated muscle. As you read this chapter, try to keep these twin concepts in mind: pump and muscle.

Although the term “heart” is an English word, cardiac (heart-related) terminology can be traced back to the Latin term, “kardia.” Cardiology is the study of the heart, and cardiologists are the physicians who deal primarily with the heart.

Figure 1. This artist’s conception of the human heart suggests a powerful engine—not inappropriate for a muscular pump that keeps the body continually supplied with blood. (credit: Patrick J. Lynch)

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Heart Anatomy

Learning Objectives

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

- Describe the location and position of the heart within the body cavity
- Describe the internal and external anatomy of the heart
- Identify the tissue layers of the heart
- Relate the structure of the heart to its function as a pump
- Compare systemic circulation to pulmonary circulation
- Identify the veins and arteries of the coronary circulation system
- Trace the pathway of oxygenated and deoxygenated blood thorough the chambers of the heart

The vital importance of the heart is obvious. If one assumes an average rate of contraction of 75 contractions per minute, a human heart would contract approximately 108,000 times in one day, more than 39 million times in one year, and nearly 3 billion times during a 75-year lifespan. Each of the major pumping chambers of the heart ejects approximately 70 mL blood per contraction in a resting adult. This would be equal to 5.25 liters of fluid per minute and approximately 14,000 liters per day. Over one year, that would equal 10,000,000 liters or 2.6 million gallons of blood sent through roughly 60,000 miles of vessels. In order to understand how that happens, it is necessary to understand the anatomy and physiology of the heart.

Location of the Heart

The human heart is located within the thoracic cavity, medially between the lungs in the space known as the mediastinum. Figure 1 shows the position of the heart within the thoracic cavity. Within the mediastinum, the heart is separated from the other mediastinal structures by a tough membrane known as the pericardium, or pericardial sac, and sits in its own space called the pericardial cavity. The dorsal surface of the heart lies near the bodies of the vertebrae, and its anterior surface sits deep to the sternum and costal cartilages. The great veins, the superior and inferior venae cavae, and the great arteries, the aorta and pulmonary trunk, are attached to the superior surface of the heart, called the base. The base of the heart is located at the level of the third costal cartilage, as seen in Figure 1. The inferior tip of the heart, the apex, lies just to the left of the sternum between the junction of the fourth and fifth ribs near their articulation with the costal cartilages. The right side of the heart is deflected anteriorly, and the left side is deflected posteriorly. It is important to remember the position and orientation of the heart when placing a stethoscope on the chest of a patient and listening for heart sounds, and also when looking at images taken from a midsagittal perspective. The slight deviation of the apex to the left is reflected in a depression in the medial surface of the inferior lobe of the left lung, called the cardiac notch.
Figure 1. The heart is located within the thoracic cavity, medially between the lungs in the mediastinum. It is about the size of a fist, is broad at the top, and tapers toward the base.

Everyday Connection: CPR

The position of the heart in the torso between the vertebrae and sternum (see the image above for the position of the heart within the thorax) allows for individuals to apply an emergency technique known as cardiopulmonary resuscitation (CPR) if the heart of a patient should stop. By applying pressure with the flat portion of one hand on the sternum in the area between the lines in the image below, it is possible to manually compress the blood within the heart enough to push some of the blood within it into the pulmonary and systemic circuits. This is particularly critical for the brain, as irreversible damage and death of neurons occur within minutes of loss of blood flow. Current standards call for compression of the chest at least 5 cm deep and at a rate of 100 compressions per minute, a rate equal to the beat in “Staying Alive,” recorded in 1977 by the Bee Gees. If you are unfamiliar with this song, you can likely find a version of it online. At this stage, the emphasis is on performing high-quality chest compressions, rather than providing artificial respiration. CPR is generally performed until the patient regains spontaneous contraction or is declared dead by an experienced healthcare professional.

When performed by untrained or overzealous individuals, CPR can result in broken ribs or a broken sternum, and can inflict additional severe damage on the patient. It is also possible, if the hands are placed too low on the sternum, to manually drive the xiphoid process into the liver, a consequence that may prove fatal for the
Anatomy

Proper training is essential. This proven life-sustaining technique is so valuable that virtually all medical personnel as well as concerned members of the public should be certified and routinely recertified in its application. CPR courses are offered at a variety of locations, including colleges, hospitals, the American Red Cross, and some commercial companies. They normally include practice of the compression technique on a mannequin.

![Figure 2. If the heart should stop, CPR can maintain the flow of blood until the heart resumes beating. By applying pressure to the sternum, the blood within the heart will be squeezed out of the heart and into the circulation. Proper positioning of the hands on the sternum to perform CPR would be between the lines at T4 and T9.]

Shape and Size of the Heart

The shape of the heart is similar to a pinecone, rather broad at the superior surface and tapering to the apex. A typical heart is approximately the size of your fist: 12 cm (5 in) in length, 8 cm (3.5 in) wide, and 6 cm (2.5 in) in thickness. Given the size difference between most members of the sexes, the weight of a female heart is approximately 250–300 grams (9 to 11 ounces), and the weight of a male heart is approximately 300–350 grams (11 to 12 ounces). The heart of a well-trained athlete, especially one specializing in aerobic sports, can be considerably larger than this. Cardiac muscle responds to exercise in a manner similar to that of skeletal muscle. That is, exercise results in the addition of protein myofilaments that increase the size of the individual cells without increasing their numbers, a concept called hypertrophy. Hearts of athletes can pump blood more effectively at lower rates than those of nonathletes. Enlarged hearts are not always a result of exercise; they can result from pathologies, such as hypertrophic cardiomyopathy. The cause of an abnormally enlarged heart muscle is unknown, but the condition is often undiagnosed and can cause sudden death in apparently otherwise healthy young people.

Chambers and Circulation through the Heart

The human heart consists of four chambers: The left side and the right side each have one atrium and one ventricle. Each of the upper chambers, the right atrium (plural = atria) and the left atrium, acts as a receiving chamber and contracts to push blood into the lower chambers, the right ventricle and the left ventricle. The ventricles serve as the primary pumping chambers of the heart, propelling blood to the lungs or to the rest of the body.

There are two distinct but linked circuits in the human circulation called the pulmonary and systemic circuits.
Although both circuits transport blood and everything it carries, we can initially view the circuits from the point of view of gases. The \textbf{pulmonary circuit} transports blood to and from the lungs, where it picks up oxygen and delivers carbon dioxide for exhalation. The \textbf{systemic circuit} transports oxygenated blood to virtually all of the tissues of the body and returns relatively deoxygenated blood and carbon dioxide to the heart to be sent back to the pulmonary circulation.

The right ventricle pumps deoxygenated blood into the \textbf{pulmonary trunk}, which leads toward the lungs and bifurcates into the left and right \textbf{pulmonary arteries}. These vessels in turn branch many times before reaching the \textbf{pulmonary capillaries}, where gas exchange occurs: Carbon dioxide exits the blood and oxygen enters. The pulmonary trunk arteries and their branches are the only arteries in the post-natal body that carry relatively deoxygenated blood. Highly oxygenated blood returning from the pulmonary capillaries in the lungs passes through a series of vessels that join together to form the \textbf{pulmonary veins}—the only post-natal veins in the body that carry highly oxygenated blood. The pulmonary veins conduct blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and on to the many branches of the systemic circuit. Eventually, these vessels will lead to the systemic capillaries, where exchange with the tissue fluid and cells of the body occurs. In this case, oxygen and nutrients exit the systemic capillaries to be used by the cells in their metabolic processes, and carbon dioxide and waste products will enter the blood.

The blood exiting the systemic capillaries is lower in oxygen concentration than when it entered. The capillaries will ultimately unite to form venules, joining to form ever-larger veins, eventually flowing into the two major systemic veins, the \textbf{superior vena cava} and the \textbf{inferior vena cava}, which return blood to the right atrium. The blood in the superior and inferior venae cavae flows into the right atrium, which pumps blood into the right ventricle. This process of blood circulation continues as long as the individual remains alive. Understanding the flow of blood through the pulmonary and systemic circuits is critical to all health professions.
Figure 3. Blood flows from the right atrium to the right ventricle, where it is pumped into the pulmonary circuit. The blood in the pulmonary artery branches is low in oxygen but relatively high in carbon dioxide. Gas exchange occurs in the pulmonary capillaries (oxygen into the blood, carbon dioxide out), and blood high in oxygen and low in carbon dioxide is returned to the left atrium. From here, blood enters the left ventricle, which pumps it into the systemic circuit. Following exchange in the systemic capillaries (oxygen and nutrients out of the capillaries and carbon dioxide and wastes in), blood returns to the right atrium and the cycle is repeated.

Membranes, Surface Features, and Layers

Our exploration of more in-depth heart structures begins by examining the membrane that surrounds the heart, the prominent surface features of the heart, and the layers that form the wall of the heart. Each of these components plays its own unique role in terms of function.
Membranes

The membrane that directly surrounds the heart and defines the pericardial cavity is called the pericardium or pericardial sac. It also surrounds the “roots” of the major vessels, or the areas of closest proximity to the heart. The pericardium, which literally translates as “around the heart,” consists of two distinct sublayers: the sturdy outer fibrous pericardium and the inner serous pericardium. The fibrous pericardium is made of tough, dense connective tissue that protects the heart and maintains its position in the thorax. The more delicate serous pericardium consists of two layers: the parietal pericardium, which is fused to the fibrous pericardium, and an inner visceral pericardium, or epicardium, which is fused to the heart and is part of the heart wall. The pericardial cavity, filled with lubricating serous fluid, lies between the epicardium and the pericardium.

In most organs within the body, visceral serous membranes such as the epicardium are microscopic. However, in the case of the heart, it is not a microscopic layer but rather a macroscopic layer, consisting of a simple squamous epithelium called a mesothelium, reinforced with loose, irregular, or areolar connective tissue that attaches to the pericardium. This mesothelium secretes the lubricating serous fluid that fills the pericardial cavity and reduces friction as the heart contracts.

Disorders of the Heart

Cardiac Tamponade

If excess fluid builds within the pericardial space, it can lead to a condition called cardiac tamponade, or pericardial tamponade. With each contraction of the heart, more fluid—in most instances, blood—accumulates within the pericardial cavity. In order to fill with blood for the next contraction, the heart must relax. However, the excess fluid in the pericardial cavity puts pressure on the heart and prevents full relaxation, so the chambers within the heart contain slightly less blood as they begin each heart cycle. Over time, less and less blood is ejected from the heart. If the fluid builds up slowly, as in hypothyroidism, the pericardial cavity may be able to expand gradually to accommodate this extra volume. Some cases of fluid in excess of one liter within the pericardial cavity have been reported. Rapid accumulation of as little as 100 mL of fluid following trauma may trigger cardiac tamponade. Other common causes include myocardial rupture, pericarditis, cancer, or even cardiac surgery. Removal of this excess fluid requires insertion of drainage tubes into the pericardial cavity. Premature removal of these drainage tubes, for example, following cardiac surgery, or clot formation within these tubes are causes of this condition. Untreated, cardiac tamponade can lead to death.
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Surface Features of the Heart

Inside the pericardium, the surface features of the heart are visible, including the four chambers. There is a superficial leaf-like extension of the atria near the superior surface of the heart, one on each side, called an **auricle**—a name that means “ear like”—because its shape resembles the external ear of a human (Figure 5). Auricles are relatively thin-walled structures that can fill with blood and empty into the atria or upper chambers of the heart. You may also hear them referred to as atrial appendages. Also prominent is a series of fat-filled grooves, each of which is known as a **sulcus** (plural = sulci), along the superior surfaces of the heart. Major coronary blood vessels are located in these sulci. The deep **coronary sulcus** is located between the atria and ventricles. Located between the left and right ventricles are two additional sulci that are not as deep as the coronary sulcus. The **anterior interventricular sulcus** is visible on the anterior surface of the heart, whereas the **posterior interventricular sulcus** is visible on the posterior surface of the heart. Figure 5 illustrates anterior and posterior views of the surface of the heart.

**Figure 5.** Inside the pericardium, the surface features of the heart are visible.

Layers

The wall of the heart is composed of three layers of unequal thickness. From superficial to deep, these are the epicardium, the myocardium, and the endocardium. The outermost layer of the wall of the heart is also the innermost layer of the pericardium, the epicardium, or the visceral pericardium discussed earlier.
The middle and thickest layer is the **myocardium**, made largely of cardiac muscle cells. It is built upon a framework of collagenous fibers, plus the blood vessels that supply the myocardium and the nerve fibers that help regulate the heart. It is the contraction of the myocardium that pumps blood through the heart and into the major arteries. The muscle pattern is elegant and complex, as the muscle cells swirl and spiral around the chambers of the heart. They form a figure 8 pattern around the atria and around the bases of the great vessels. Deeper ventricular muscles also form a figure 8 around the two ventricles and proceed toward the apex. More superficial layers of ventricular muscle wrap around both ventricles. This complex swirling pattern allows the heart to pump blood more effectively than a simple linear pattern would. Figure 6 illustrates the arrangement of muscle cells.

Although the ventricles on the right and left sides pump the same amount of blood per contraction, the muscle of the left ventricle is much thicker and better developed than that of the right ventricle. In order to overcome the high resistance required to pump blood into the long systemic circuit, the left ventricle must generate a great amount of pressure. The right ventricle does not need to generate as much pressure, since the pulmonary circuit is shorter and provides less resistance. The image below illustrates the differences in muscular thickness needed for each of the ventricles.

The innermost layer of the heart wall, the **endocardium**, is joined to the myocardium with a thin layer of connective tissue. The endocardium lines the chambers where the blood circulates and covers the heart valves. It is made of simple squamous epithelium called **endothelium**, which is continuous with the endothelial lining of the blood vessels.

Once regarded as a simple lining layer, recent evidence indicates that the endothelium of the endocardium and the coronary capillaries may play active roles in regulating the contraction of the muscle within the myocardium. The endothelium may also regulate the growth patterns of the cardiac muscle cells throughout life, and the endothelins it secretes create an environment in the surrounding tissue fluids that regulates ionic concentrations.
and states of contractility. Endothelins are potent vasoconstrictors and, in a normal individual, establish a homeostatic balance with other vasoconstrictors and vasodilators.

Internal Structure of the Heart

Recall that the heart’s contraction cycle follows a dual pattern of circulation—the pulmonary and systemic circuits—because of the pairs of chambers that pump blood into the circulation. In order to develop a more precise understanding of cardiac function, it is first necessary to explore the internal anatomical structures in more detail.

Septa of the Heart

The word septum is derived from the Latin for “something that encloses;” in this case, a septum (plural = septa) refers to a wall or partition that divides the heart into chambers. The septa are physical extensions of the myocardium lined with endocardium. Located between the two atria is the interatrial septum. Normally in an adult heart, the interatrial septum bears an oval-shaped depression known as the fossa ovalis, a remnant of an opening in the fetal heart known as the foramen ovale. The foramen ovale allowed blood in the fetal heart to pass directly from the right atrium to the left atrium, allowing some blood to bypass the pulmonary circuit. Within seconds after birth, a flap of tissue known as the septum primum that previously acted as a valve closes the foramen ovale and establishes the typical cardiac circulation pattern.

Between the two ventricles is a second septum known as the interventricular septum. Unlike the interatrial septum, the interventricular septum is normally intact after its formation during fetal development. It is substantially thicker than the interatrial septum, since the ventricles generate far greater pressure when they contract.

The septum between the atria and ventricles is known as the atrioventricular septum. It is marked by the presence of four openings that allow blood to move from the atria into the ventricles and from the ventricles into the pulmonary trunk and aorta. Located in each of these openings between the atria and ventricles is a valve, a specialized structure that ensures one-way flow of blood. The valves between the atria and ventricles are known generically as atrioventricular valves. The valves at the openings that lead to the pulmonary trunk and aorta are known generically as semilunar valves. The interventricular septum is visible in the image below. In this figure, the atrioventricular septum has been removed to better show the bicupid and tricuspid valves; the interatrial septum is not visible, since its location is covered by the aorta and pulmonary trunk. Since these openings and valves structurally weaken the atrioventricular septum, the remaining tissue is heavily reinforced with dense connective tissue called the cardiac skeleton, or skeleton of the heart. It includes four rings that surround the openings between the atria and ventricles, and the openings to the pulmonary trunk and aorta, and serve as the point of attachment for the heart valves. The cardiac skeleton also provides an important boundary in the heart electrical conduction system.
Disorders of the Heart: Heart Defects

One very common form of interatrial septum pathology is patent foramen ovale, which occurs when the septum primum does not close at birth, and the fossa ovalis is unable to fuse. The word patent is from the Latin root patens for “open.” It may be benign or asymptomatic, perhaps never being diagnosed, or in extreme cases, it may require surgical repair to close the opening permanently. As much as 20–25 percent of the general population may have a patent foramen ovale, but fortunately, most have the benign, asymptomatic version. Patent foramen ovale is normally detected by auscultation of a heart murmur (an abnormal heart sound) and confirmed by imaging with an echocardiogram. Despite its prevalence in the general population, the causes of patent ovale are unknown, and there are no known risk factors. In nonlife-threatening cases, it is better to monitor the condition than to risk heart surgery to repair and seal the opening.

Coarctation of the aorta is a congenital abnormal narrowing of the aorta that is normally located at the insertion of the ligamentum arteriosum, the remnant of the fetal shunt called the ductus arteriosus. If severe, this condition drastically restricts blood flow through the primary systemic artery, which is life threatening. In some individuals, the condition may be fairly benign and not detected until later in life. Detectable symptoms in an infant include difficulty breathing, poor appetite, trouble feeding, or failure to thrive. In older individuals, symptoms include dizziness, fainting, shortness of breath, chest pain, fatigue, headache, and nosebleeds. Treatment involves surgery to resect (remove) the affected region or angioplasty to open the abnormally narrow passageway. Studies have shown that the earlier the surgery is performed, the better the chance of survival.

A patent ductus arteriosus is a congenital condition in which the ductus arteriosus fails to close. The condition may range from severe to benign. Failure of the ductus arteriosus to close results in blood flowing from the higher pressure aorta into the lower pressure pulmonary trunk. This additional fluid moving toward the lungs increases pulmonary pressure and makes respiration difficult. Symptoms include shortness of breath (dyspnea), tachycardia, enlarged heart, a widened pulse pressure, and poor weight gain in infants. Treatments include surgical closure (ligation), manual closure using platinum coils or specialized mesh inserted via the femoral artery or vein, or nonsteroidal anti-inflammatory drugs to block the synthesis of prostaglandin E2, which maintains the vessel in an open position. If untreated, the condition can result in congestive heart failure.

Septal defects are not uncommon in individuals and may be congenital or caused by various disease processes. Tetralogy of Fallot is a congenital condition that may also occur from exposure to unknown environmental factors; it occurs when there is an opening in the interventricular septum caused by blockage of the pulmonary
trunk, normally at the pulmonary semilunar valve. This allows blood that is relatively low in oxygen from the right ventricle to flow into the left ventricle and mix with the blood that is relatively high in oxygen. Symptoms include a distinct heart murmur, low blood oxygen percent saturation, dyspnea or difficulty in breathing, polycythemia, broadening (clubbing) of the fingers and toes, and in children, difficulty in feeding or failure to grow and develop. It is the most common cause of cyanosis following birth. The term “tetralogy” is derived from the four components of the condition, although only three may be present in an individual patient: pulmonary infundibular stenosis (rigidity of the pulmonary valve), overriding aorta (the aorta is shifted above both ventricles), ventricular septal defect (opening), and right ventricular hypertrophy (enlargement of the right ventricle). Other heart defects may also accompany this condition, which is typically confirmed by echocardiography imaging. Tetralogy of Fallot occurs in approximately 400 out of one million live births. Normal treatment involves extensive surgical repair, including the use of stents to redirect blood flow and replacement of valves and patches to repair the septal defect, but the condition has a relatively high mortality. Survival rates are currently 75 percent during the first year of life; 60 percent by 4 years of age; 30 percent by 10 years; and 5 percent by 40 years.

In the case of severe septal defects, including both tetralogy of Fallot and patent foramen ovale, failure of the heart to develop properly can lead to a condition commonly known as a “blue baby.” Regardless of normal skin pigmentation, individuals with this condition have an insufficient supply of oxygenated blood, which leads to cyanosis, a blue or purple coloration of the skin, especially when active. Septal defects are commonly first detected through auscultation, listening to the chest using a stethoscope. In this case, instead of hearing normal heart sounds attributed to the flow of blood and closing of heart valves, unusual heart sounds may be detected. This is often followed by medical imaging to confirm or rule out a diagnosis. In many cases, treatment may not be needed. Some common congenital heart defects are illustrated in Figure 9.

![Figure 9](image)

*Figure 9. (a) A patent foramen ovale defect is an abnormal opening in the interatrial septum, or more commonly, a failure of the foramen ovale to close. (b) Coarctation of the aorta is an abnormal narrowing of the aorta. (c) A patent ductus arteriosus is the failure of the ductus arteriosus to close. (d) Tetralogy of Fallot includes an abnormal opening in the interventricular septum.*

**Right Atrium**

The right atrium serves as the receiving chamber for blood returning to the heart from the systemic circulation. The two major systemic veins, the superior and inferior venae cavae, and the large coronary vein called the **coronary sinus** that drains the heart myocardium empty into the right atrium. The superior vena cava drains blood from regions superior to the diaphragm: the head, neck, upper limbs, and the thoracic region. It empties into the superior and posterior portions of the right atrium. The inferior vena cava drains blood from areas inferior to the diaphragm: the lower limbs and abdominopelvic region of the body. It, too, empties into the posterior
portion of the atria, but inferior to the opening of the superior vena cava. Immediately superior and slightly medial to the opening of the inferior vena cava on the posterior surface of the atrium is the opening of the coronary sinus. This thin-walled vessel drains most of the coronary veins that return systemic blood from the heart. The majority of the internal heart structures discussed in this and subsequent sections are illustrated in Figure 8.

While the bulk of the internal surface of the right atrium is smooth, the depression of the fossa ovalis is medial, and the anterior surface demonstrates prominent ridges of muscle called the **pectinate muscles**. The right auricle also has pectinate muscles. The left atrium does not have pectinate muscles except in the auricle.

The atria receive venous blood on a nearly continuous basis, preventing venous flow from stopping while the ventricles are contracting. While most ventricular filling occurs while the atria are relaxed, they do demonstrate a contractile phase and actively pump blood into the ventricles just prior to ventricular contraction. The opening between the atrium and ventricle is guarded by the tricuspid valve.

Right Ventricle

The right ventricle receives blood from the right atrium through the tricuspid valve. Each flap of the valve is attached to strong strands of connective tissue, the **chordae tendineae**, literally “tendinous cords,” or sometimes more poetically referred to as “heart strings.” There are several chordae tendineae associated with each of the flaps. They are composed of approximately 80 percent collagenous fibers with the remainder consisting of elastic fibers and endothelium. They connect each of the flaps to a **papillary muscle** that extends from the inferior ventricular surface. There are three papillary muscles in the right ventricle, called the anterior, posterior, and septal muscles, which correspond to the three sections of the valves.

When the myocardium of the ventricle contracts, pressure within the ventricular chamber rises. Blood, like any fluid, flows from higher pressure to lower pressure areas, in this case, toward the pulmonary trunk and the atrium. To prevent any potential backflow, the papillary muscles also contract, generating tension on the chordae tendineae. This prevents the flaps of the valves from being forced into the atria and regurgitation of the blood back into the atria during ventricular contraction. The image below shows papillary muscles and chordae tendineae attached to the tricuspid valve.

![Figure 10. In this frontal section, you can see papillary muscles attached to the tricuspid valve on the right as well as the mitral valve on the left via chordae tendineae. (credit: modification of work by “PV KS”/flickr.com)](image)

The walls of the ventricle are lined with **trabeculae carneae**, ridges of cardiac muscle covered by endocardium. In addition to these muscular ridges, a band of cardiac muscle, also covered by endocardium, known as the **moderator band** reinforces the thin walls of the right ventricle and plays a crucial role in cardiac conduction. It arises from the inferior portion of the interventricular septum and crosses the interior space of the right ventricle to connect with the inferior papillary muscle.

When the right ventricle contracts, it ejects blood into the pulmonary trunk, which branches into the left and right
pulmonary arteries that carry it to each lung. The superior surface of the right ventricle begins to taper as it approaches the pulmonary trunk. At the base of the pulmonary trunk is the pulmonary semilunar valve that prevents backflow from the pulmonary trunk.

**Left Atrium**

After exchange of gases in the pulmonary capillaries, blood returns to the left atrium high in oxygen via one of the four pulmonary veins. While the left atrium does not contain pectinate muscles, it does have an auricle that includes these pectinate ridges. Blood flows nearly continuously from the pulmonary veins back into the atrium, which acts as the receiving chamber, and from here through an opening into the left ventricle. Most blood flows passively into the heart while both the atria and ventricles are relaxed, but toward the end of the ventricular relaxation period, the left atrium will contract, pumping blood into the ventricle. This atrial contraction accounts for approximately 20 percent of ventricular filling. The opening between the left atrium and ventricle is guarded by the mitral valve.

**Left Ventricle**

Recall that, although both sides of the heart will pump the same amount of blood, the muscular layer is much thicker in the left ventricle compared to the right. Like the right ventricle, the left also has trabeculae carneae, but there is no moderator band. The mitral valve is connected to papillary muscles via chordae tendineae. There are two papillary muscles on the left—the anterior and posterior—as opposed to three on the right.

The left ventricle is the major pumping chamber for the systemic circuit; it ejects blood into the aorta through the aortic semilunar valve.

**Heart Valve Structure and Function**

A transverse section through the heart slightly above the level of the atrioventricular septum reveals all four heart valves along the same plane (Figure 11). The valves ensure unidirectional blood flow through the heart. Between the right atrium and the right ventricle is the **right atrioventricular valve**, or **tricuspid valve**. It typically consists of three flaps, or leaflets, made of endocardium reinforced with additional connective tissue. The flaps are connected by chordae tendineae to the papillary muscles, which control the opening and closing of the valves.

Emerging from the right ventricle at the base of the pulmonary trunk is the **pulmonary valve**; it is also known as the pulmonic valve or the right semilunar valve. The pulmonary valve is comprised of three small flaps of endothelium reinforced with connective tissue. When the ventricle relaxes, the pressure differential causes blood to flow back into the ventricle from the pulmonary trunk. This flow of blood fills the pocket-like flaps of the pulmonary valve, causing the valve to close and producing an audible sound. Unlike the atrioventricular valves, there are no papillary muscles or chordae tendineae associated with the pulmonary valve.

*Figure 11. With the atria and major vessels removed, all four valves are clearly visible, although it is difficult to distinguish the three separate cusps of the tricuspid valve.*
Located at the opening between the left atrium and left ventricle is the **mitral valve**, also called the **bicuspide valve** or the **left atrioventricular valve**. Structurally, this valve consists of two cusps, known as the anterior medial cusp and the posterior medial cusp, compared to the three cusps of the tricuspid valve. In a clinical setting, the valve is referred to as the mitral valve, rather than the bicuspid valve. The two cusps of the mitral valve are attached by chordae tendineae to two papillary muscles that project from the wall of the ventricle.

At the base of the aorta is the aortic semilunar valve, or the **aortic valve**, which prevents backflow from the aorta. It normally is composed of three flaps. When the ventricle relaxes and blood attempts to flow back into the ventricle from the aorta, blood will fill the cusps of the valve, causing it to close and producing an audible sound.

In the image above, the two atrioventricular valves are open and the two semilunar valves are closed. This occurs when both atria and ventricles are relaxed and when the atria contract to pump blood into the ventricles. The image below shows a frontal view. Although only the left side of the heart is illustrated, the process is virtually identical on the right.

![Figure 12. (a) A transverse section through the heart illustrates the four heart valves. The two atrioventricular valves are open; the two semilunar valves are closed. The atria and vessels have been removed. (b) A frontal section through the heart illustrates blood flow through the mitral valve. When the mitral valve is open, it allows blood to move from the left atrium to the left ventricle. The aortic semilunar valve is closed to prevent backflow of blood from the aorta to the left ventricle. Image a above shows the atrioventricular valves closed while the two semilunar valves are open. This occurs when the ventricles contract to eject blood into the pulmonary trunk and aorta. Closure of the two atrioventricular valves prevents blood from being forced back into the atria. This stage can be seen from a frontal view in image b above.](image)
Anatomy

Figure 13. (a) A transverse section through the heart illustrates the four heart valves during ventricular contraction. The two atrioventricular valves are closed, but the two semilunar valves are open. The atria and vessels have been removed. (b) A frontal view shows the closed mitral (bicuspid) valve that prevents backflow of blood into the left atrium. The aortic semilunar valve is open to allow blood to be ejected into the aorta.

When the ventricles begin to contract, pressure within the ventricles rises and blood flows toward the area of lowest pressure, which is initially in the atria. This backflow causes the cusps of the tricuspid and mitral (bicuspid) valves to close. These valves are tied down to the papillary muscles by chordae tendineae. During the relaxation phase of the cardiac cycle, the papillary muscles are also relaxed and the tension on the chordae tendineae is slight (image b above). However, as the myocardium of the ventricle contracts, so do the papillary muscles. This creates tension on the chordae tendineae (image b above), helping to hold the cusps of the atrioventricular valves in place and preventing them from being blown back into the atria.

The aortic and pulmonary semilunar valves lack the chordae tendineae and papillary muscles associated with the atrioventricular valves. Instead, they consist of pocket-like folds of endocardium reinforced with additional connective tissue. When the ventricles relax and the change in pressure forces the blood toward the ventricles, the blood presses against these cusps and seals the openings.

Practice Question

Figure 14 (in online textbook) shows an echocardiogram of actual heart valves opening and closing. Although much of the heart has been “removed” from this gif loop so the chordae tendineae are not visible, why is their presence more critical for the atrioventricular valves (tricuspid and mitral) than the semilunar (aortic and pulmonary) valves?
Disorders of the Heart Valves

When heart valves do not function properly, they are often described as incompetent and result in valvular heart disease, which can range from benign to lethal. Some of these conditions are congenital, that is, the individual was born with the defect, whereas others may be attributed to disease processes or trauma. Some malfunctions are treated with medications, others require surgery, and still others may be mild enough that the condition is merely monitored since treatment might trigger more serious consequences.

Valvular disorders are often caused by carditis, or inflammation of the heart. One common trigger for this inflammation is rheumatic fever, or scarlet fever, an autoimmune response to the presence of a bacterium, Streptococcus pyogenes, normally a disease of childhood.

While any of the heart valves may be involved in valve disorders, mitral regurgitation is the most common, detected in approximately 2 percent of the population, and the pulmonary semilunar valve is the least frequently involved. When a valve malfunctions, the flow of blood to a region will often be disrupted. The resulting inadequate flow of blood to this region will be described in general terms as an insufficiency. The specific type of insufficiency is named for the valve involved: aortic insufficiency, mitral insufficiency, tricuspid insufficiency, or pulmonary insufficiency.

If one of the cusps of the valve is forced backward by the force of the blood, the condition is referred to as a prolapsed valve. Prolapse may occur if the chordae tendineae are damaged or broken, causing the closure mechanism to fail. The failure of the valve to close properly disrupts the normal one-way flow of blood and results in regurgitation, when the blood flows backward from its normal path. Using a stethoscope, the disruption to the normal flow of blood produces a heart murmur.

Stenosis is a condition in which the heart valves become rigid and may calcify over time. The loss of flexibility of the valve interferes with normal function and may cause the heart to work harder to propel blood through the valve, which eventually weakens the heart. Aortic stenosis affects approximately 2 percent of the population over 65 years of age, and the percentage increases to approximately 4 percent in individuals over 85 years. Occasionally, one or more of the chordae tendineae will tear or the papillary muscle itself may die as a component of a myocardial infarction (heart attack). In this case, the patient’s condition will deteriorate dramatically and rapidly, and immediate surgical intervention may be required.

Auscultation, or listening to a patient’s heart sounds, is one of the most useful diagnostic tools, since it is proven, safe, and inexpensive. The term auscultation is derived from the Latin for “to listen,” and the technique has been used for diagnostic purposes as far back as the ancient Egyptians. Valve and septal disorders will trigger abnormal heart sounds. If a valvular disorder is detected or suspected, a test called an echocardiogram, or simply an “echo,” may be ordered. Echocardiograms are sonograms of the heart and can help in the diagnosis of valve disorders as well as a wide variety of heart pathologies.

Career Connection: Cardiologist

Cardiologists are medical doctors that specialize in the diagnosis and treatment of diseases of the heart. After completing 4 years of medical school, cardiologists complete a three-year residency in internal medicine followed by an additional three or more years in cardiology. Following this 10-year period of medical training and clinical experience, they qualify for a rigorous two-day examination administered by the Board of Internal Medicine that tests their academic training and clinical abilities, including diagnostics and treatment. After successful completion of this examination, a physician becomes a board-certified cardiologist. Some board-certified cardiologists may be invited to become a Fellow of the American College of Cardiology (FACC). This professional recognition is awarded to outstanding physicians based upon merit, including outstanding credentials, achievements, and community contributions to cardiovascular medicine.
Career Connection: Cardiovascular Technologist/Technician

Cardiovascular technologists/technicians are trained professionals who perform a variety of imaging techniques, such as sonograms or echocardiograms, used by physicians to diagnose and treat diseases of the heart. Nearly all of these positions require an associate degree, and these technicians earn a median salary of $49,410 as of May 2010, according to the U.S. Bureau of Labor Statistics. Growth within the field is fast, projected at 29 percent from 2010 to 2020. There is a considerable overlap and complementary skills between cardiac technicians and vascular technicians, and so the term cardiovascular technician is often used. Special certifications within the field require documenting appropriate experience and completing additional and often expensive certification examinations. These subspecialties include Certified Rhythm Analysis Technician (CRAT), Certified Cardiographic Technician (CCT), Registered Congenital Cardiac Sonographer (RCCS), Registered Cardiac Electrophysiology Specialist (RCES), Registered Cardiovascular Invasive Specialist (RCIS), Registered Cardiac Sonographer (RCS), Registered Vascular Specialist (RVS), and Registered Phlebology Sonographer (RPhS).

Coronary Circulation

You will recall that the heart is a remarkable pump composed largely of cardiac muscle cells that are incredibly active throughout life. Like all other cells, a cardiomyocyte requires a reliable supply of oxygen and nutrients, and a way to remove wastes, so it needs a dedicated, complex, and extensive coronary circulation. And because of the critical and nearly ceaseless activity of the heart throughout life, this need for a blood supply is even greater than for a typical cell. However, coronary circulation is not continuous; rather, it cycles, reaching a peak when the heart muscle is relaxed and nearly ceasing while it is contracting.

Coronary Arteries

Coronary arteries supply blood to the myocardium and other components of the heart. The first portion of the aorta after it arises from the left ventricle gives rise to the coronary arteries. There are three dilations in the wall of the aorta just superior to the aortic semilunar valve. Two of these, the left posterior aortic sinus and anterior aortic sinus, give rise to the left and right coronary arteries, respectively. The third sinus, the right posterior aortic sinus, typically does not give rise to a vessel. Coronary vessel branches that remain on the surface of the artery and follow the sulci are called epicardial coronary arteries.

The left coronary artery distributes blood to the left side of the heart, the left atrium and ventricle, and the interventricular septum. The circumflex artery arises from the left coronary artery and follows the coronary sulcus to the left. Eventually, it will fuse with the small branches of the right coronary artery. The larger anterior interventricular artery, also known as the left anterior descending artery (LAD), is the second major branch arising from the left coronary artery. It follows the anterior interventricular sulcus around the pulmonary trunk. Along the way it gives rise to numerous smaller branches that interconnect with the branches of the posterior interventricular artery, forming anastomoses. An anastomosis is an area where vessels unite to form interconnections that normally allow blood to circulate to a region even if there may be partial blockage in another branch. The anastomoses in the heart are very small. Therefore, this ability is somewhat restricted in the heart so a coronary artery blockage often results in death of the cells (myocardial infarction) supplied by the particular vessel.

The right coronary artery proceeds along the coronary sulcus and distributes blood to the right atrium, portions of both ventricles, and the heart conduction system. Normally, one or more marginal arteries arise from the right coronary artery inferior to the right atrium. The marginal arteries supply blood to the superficial portions of the right ventricle. On the posterior surface of the heart, the right coronary artery gives rise to the posterior interventricular artery, also known as the posterior descending artery. It runs along the posterior portion of the interventricular sulcus toward the apex of the heart, giving rise to branches that supply the interventricular septum and portions of both ventricles. Figure 15 presents views of the coronary circulation from both the anterior and posterior views.
Diseases of the Heart: Myocardial Infarction

Myocardial infarction (MI) is the formal term for what is commonly referred to as a heart attack. It normally results from a lack of blood flow (ischemia) and oxygen (hypoxia) to a region of the heart, resulting in death of the cardiac muscle cells. An MI often occurs when a coronary artery is blocked by the buildup of atherosclerotic plaque consisting of lipids, cholesterol and fatty acids, and white blood cells, primarily macrophages. It can also occur when a portion of an unstable atherosclerotic plaque travels through the coronary arterial system and lodges in one of the smaller vessels. The resulting blockage restricts the flow of blood and oxygen to the myocardium and causes death of the tissue. MIs may be triggered by excessive exercise, in which the partially occluded artery is no longer able to pump sufficient quantities of blood, or severe stress, which may induce spasm of the smooth muscle in the walls of the vessel. In the case of acute MI, there is often sudden pain beneath the sternum (retrosternal pain) called angina pectoris, often radiating down the left arm in males but not in female patients. Until this anomaly between the sexes was discovered, many female patients suffering MIs were misdiagnosed and sent home. In addition, patients typically present with difficulty breathing and shortness of breath (dyspnea), irregular heartbeat (palpations), nausea and vomiting, sweating (diaphoresis), anxiety, and fainting (syncope), although not all of these symptoms may be present. Many of the symptoms are shared with other medical conditions, including anxiety attacks and simple indigestion, so differential diagnosis is critical. It is estimated that between 22 and 64 percent of MIs present without any symptoms. An MI can be confirmed by examining the patient’s ECG, which frequently reveals alterations in the ST and Q components. Some classification schemes of MI are referred to as ST-elevated MI (STEMI) and non-elevated
MI (non-STEMI). In addition, echocardiography or cardiac magnetic resonance imaging may be employed. Common blood tests indicating an MI include elevated levels of creatine kinase MB (an enzyme that catalyzes the conversion of creatine to phosphocreatine, consuming ATP) and cardiac troponin (the regulatory protein for muscle contraction), both of which are released by damaged cardiac muscle cells. Immediate treatments for MI are essential and include administering supplemental oxygen, aspirin that helps to break up clots, and nitroglycerine administered sublingually (under the tongue) to facilitate its absorption. Despite its unquestioned success in treatments and use since the 1880s, the mechanism of nitroglycerine is still incompletely understood but is believed to involve the release of nitric oxide, a known vasodilator, and endothelium-derived releasing factor, which also relaxes the smooth muscle in the tunica media of coronary vessels. Longer-term treatments include injections of thrombolytic agents such as streptokinase that dissolve the clot, the anticoagulant heparin, balloon angioplasty and stents to open blocked vessels, and bypass surgery to allow blood to pass around the site of blockage. If the damage is extensive, coronary replacement with a donor heart or coronary assist device, a sophisticated mechanical device that supplements the pumping activity of the heart, may be employed. Despite the attention, development of artificial hearts to augment the severely limited supply of heart donors has proven less than satisfactory but will likely improve in the future. MIs may trigger cardiac arrest, but the two are not synonymous. Important risk factors for MI include cardiovascular disease, age, smoking, high blood levels of the low-density lipoprotein (LDL, often referred to as “bad” cholesterol), low levels of high-density lipoprotein (HDL, or “good” cholesterol), hypertension, diabetes mellitus, obesity, lack of physical exercise, chronic kidney disease, excessive alcohol consumption, and use of illegal drugs.

**Coronary Veins**

**Coronary veins** drain the heart and generally parallel the large surface arteries. The **great cardiac vein** can be seen initially on the surface of the heart following the interventricular sulcus, but it eventually flows along the coronary sulcus into the coronary sinus on the posterior surface. The great cardiac vein initially parallels the anterior interventricular artery and drains the areas supplied by this vessel. It receives several major branches, including the posterior cardiac vein, the middle cardiac vein, and the small cardiac vein. The **posterior cardiac vein** parallels and drains the areas supplied by the marginal artery branch of the circumflex artery. The **middle cardiac vein** parallels and drains the areas supplied by the posterior interventricular artery. The **small cardiac vein** parallels the right coronary artery and drains the blood from the posterior surfaces of the right atrium and ventricle. The coronary sinus is a large, thin-walled vein on the posterior surface of the heart lying within the atrioventricular sulcus and emptying directly into the right atrium. The **anterior cardiac veins** parallel the small cardiac arteries and drain the anterior surface of the right ventricle. Unlike these other cardiac veins, it bypasses the coronary sinus and drains directly into the right atrium.

**Examples**

**Diseases of the Heart: Coronary Artery Disease**

Coronary artery disease is the leading cause of death worldwide. It occurs when the buildup of plaque—a fatty material including cholesterol, connective tissue, white blood cells, and some smooth muscle cells—within the walls of the arteries obstructs the flow of blood and decreases the flexibility or compliance of the vessels. This condition is called atherosclerosis, a hardening of the arteries that involves the accumulation of plaque. As the coronary blood vessels become occluded, the flow of blood to the tissues will be restricted, a condition called ischemia that causes the cells to receive insufficient amounts of oxygen, called hypoxia. The image below shows the blockage of coronary arteries highlighted by the injection of dye. Some individuals with coronary artery disease report pain radiating from the chest called angina pectoris, but others remain asymptomatic. If untreated, coronary artery disease can lead to MI or a heart attack.
The disease progresses slowly and often begins in children and can be seen as fatty “streaks” in the vessels. It then gradually progresses throughout life. Well-documented risk factors include smoking, family history, hypertension, obesity, diabetes, high alcohol consumption, lack of exercise, stress, and hyperlipidemia or high circulating levels of lipids in the blood. Treatments may include medication, changes to diet and exercise, angioplasty with a balloon catheter, insertion of a stent, or coronary bypass procedure.

Angioplasty is a procedure in which the occlusion is mechanically widened with a balloon. A specialized catheter with an expandable tip is inserted into a superficial vessel, normally in the leg, and then directed to the site of the occlusion. At this point, the balloon is inflated to compress the plaque material and to open the vessel to increase blood flow. Then, the balloon is deflated and retracted. A stent consisting of a specialized mesh is typically inserted at the site of occlusion to reinforce the weakened and damaged walls. Stent insertions have been routine in cardiology for more than 40 years.

Coronary bypass surgery may also be performed. This surgical procedure grafts a replacement vessel obtained from another, less vital portion of the body to bypass the occluded area. This procedure is clearly effective in treating patients experiencing a MI, but overall does not increase longevity. Nor does it seem advisable in patients with stable although diminished cardiac capacity since frequently loss of mental acuity occurs following the procedure. Long-term changes to behavior, emphasizing diet and exercise plus a medicine regime tailored to lower blood pressure, lower cholesterol and lipids, and reduce clotting are equally as effective.

**Chapter Review**

The heart resides within the pericardial sac and is located in the mediastinal space within the thoracic cavity. The pericardial sac consists of two fused layers: an outer fibrous capsule and an inner parietal pericardium lined with a serous membrane. Between the pericardial sac and the heart is the pericardial cavity, which is filled with lubricating serous fluid. The walls of the heart are composed of an outer epicardium, a thick myocardium, and an inner lining layer of endocardium. The human heart consists of a pair of atria, which receive blood and pump it into a pair of ventricles, which pump blood into the vessels. The right atrium receives systemic blood relatively low in oxygen and pumps it into the right ventricle, which pumps it into the pulmonary circuit. Exchange of oxygen and carbon dioxide occurs in the lungs, and blood high in oxygen returns to the left atrium, which pumps blood into the left ventricle, which in turn pumps blood into the aorta and the remainder of the systemic circuit. The septa are the partitions that separate the chambers of the heart. They include the interatrial septum, the interventricular septum, and the atrioventricular septum. Two of these openings are guarded by the atrioventricular valves, the right tricuspid valve and the left mitral valve, which prevent the backflow of blood. Each is attached to chordae tendineae that extend to the papillary muscles, which are extensions of the myocardium, to prevent the valves from being blown back into the atria. The pulmonary valve is located at the base of the pulmonary trunk, and the left semilunar valve is located at the base of the aorta. The right and left coronary arteries are the first to branch off the aorta and arise from two of the three sinuses located near the base.
of the aorta and are generally located in the sulci. Cardiac veins parallel the small cardiac arteries and generally drain into the coronary sinus.

**Critical Thinking Questions**

Describe how the valves keep the blood moving in one direction.
Why is the pressure in the pulmonary circulation lower than in the systemic circulation?

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Development of the Heart

Learning Objectives

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

- Describe the embryological development of heart structures
- Identify five regions of the fetal heart
- Relate fetal heart structures to adult counterparts

The human heart is the first functional organ to develop. It begins beating and pumping blood around day 21 or 22, a mere three weeks after fertilization. This emphasizes the critical nature of the heart in distributing blood through the vessels and the vital exchange of nutrients, oxygen, and wastes both to and from the developing baby. The critical early development of the heart is reflected by the prominent heart bulge that appears on the anterior surface of the embryo.

The heart forms from an embryonic tissue called mesoderm around 18 to 19 days after fertilization. Mesoderm is one of the three primary germ layers that differentiates early in development that collectively gives rise to all subsequent tissues and organs. The heart begins to develop near the head of the embryo in a region known as the cardiogenic area. Following chemical signals called factors from the underlying endoderm (another of the three primary germ layers), the cardiogenic area begins to form two strands called the cardiogenic cords. As the cardiogenic cords develop, a lumen rapidly develops within them. At this point, they are referred to as endocardial tubes. The two tubes migrate together and fuse to form a single primitive heart tube. The primitive heart tube quickly forms five distinct regions. From head to tail, strong include the truncus arteriosus, bulbus cordis, primitive ventricle, primitive atrium, and the sinus venosus. Initially, all venous blood flows into the sinus venosus, and contractions propel the blood from tail to head, or from the sinus venosus to the truncus arteriosus. This is a very different pattern from that of an adult.
Figure 1. This diagram outlines the embryological development of the human heart during the first eight weeks and the subsequent formation of the four heart chambers.

The five regions of the primitive heart tube develop into recognizable structures in a fully developed heart. The truncus arteriosus will eventually divide and give rise to the ascending aorta and pulmonary trunk. The bulbus cordis develops into the right ventricle. The primitive ventricle forms the left ventricle. The primitive atrium becomes the anterior portions of both the right and left atria, and the two auricles. The sinus venosus develops into the posterior portion of the right atrium, the SA node, and the coronary sinus.

As the primitive heart tube elongates, it begins to fold within the pericardium, eventually forming an S shape, which places the chambers and major vessels into an alignment similar to the adult heart. This process occurs between days 23 and 28. The remainder of the heart development pattern includes development of septa and valves, and remodeling of the actual chambers. Partitioning of the atria and ventricles by the interatrial septum, interventricular septum, and atrioventricular septum is complete by the end of the fifth week, although the fetal blood shunts remain until birth or shortly after. The atrioventricular valves form between weeks five and eight, and the semilunar valves form between weeks five and nine.

Chapter Review

The heart is the first organ to form and become functional, emphasizing the importance of transport of material to and from the developing infant. It originates about day 18 or 19 from the mesoderm and begins beating and pumping blood about day 21 or 22. It forms from the cardiogenic region near the head and is visible as a prominent heart bulge on the surface of the embryo. Originally, it consists of a pair of strands called cardiogenic cords that quickly form a hollow lumen and are referred to as endocardial tubes. These then fuse into a single
heart tube and differentiate into the truncus arteriosus, bulbus cordis, primitive ventricle, primitive atrium, and sinus venosus, starting about day 22. The primitive heart begins to form an S shape within the pericardium between days 23 and 28. The internal septa begin to form about day 28, separating the heart into the atria and ventricles, although the foramen ovale persists until shortly after birth. Between weeks five and eight, the atrioventricular valves form. The semilunar valves form between weeks five and nine.

Critical Thinking Questions

Why is it so important for the human heart to develop early and begin functioning within the developing embryo?

Describe how the major pumping chambers, the ventricles, form within the developing heart.

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Section 18: The Cardiovascular System: Blood Vessels and Circulation
Introduction to the Cardiovascular System: Blood Vessels and Circulation

Learning Objectives

After studying this chapter, you will be able to:

- Compare and contrast the anatomical structure of arteries, arterioles, capillaries, venules, and veins
- Accurately describe the forces that account for capillary exchange
- List the major factors affecting blood flow, blood pressure, and resistance
- Describe how blood flow, blood pressure, and resistance interrelate
- Discuss how the neural and endocrine mechanisms maintain homeostasis within the blood vessels
- Describe the interaction of the cardiovascular system with other body systems
- Label the major blood vessels of the pulmonary and systemic circulations
- Identify and describe the hepatic portal system
- Describe the development of blood vessels and fetal circulation
- Compare fetal circulation to that of an individual after birth

Figure 1. While most blood vessels are located deep from the surface and are not visible, the superficial veins of the upper limb provide an indication of the extent, prominence, and importance of these structures to the body. (credit: Colin Davis)

In this chapter, you will learn about the vascular part of the cardiovascular system, that is, the vessels that transport blood throughout the body and provide the physical site where gases, nutrients, and other substances
are exchanged with body cells. When vessel functioning is reduced, blood-borne substances do not circulate
effectively throughout the body. As a result, tissue injury occurs, metabolism is impaired, and the functions of
every bodily system are threatened.

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Structure and Function of Blood Vessels

Learning Objectives

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

- Compare and contrast the three tunics that make up the walls of most blood vessels
- Distinguish between elastic arteries, muscular arteries, and arterioles on the basis of structure, location, and function
- Describe the basic structure of a capillary bed, from the supplying metarteriole to the venule into which it drains
- Explain the structure and function of venous valves in the large veins of the extremities

Blood is carried through the body via blood vessels. An artery is a blood vessel that carries blood away from the heart, where it branches into ever-smaller vessels. Eventually, the smallest arteries, vessels called arterioles, further branch into tiny capillaries, where nutrients and wastes are exchanged, and then combine with other vessels that exit capillaries to form venules, small blood vessels that carry blood to a vein, a larger blood vessel that returns blood to the heart.

Arteries and veins transport blood in two distinct circuits: the systemic circuit and the pulmonary circuit. Systemic arteries provide blood rich in oxygen to the body’s tissues. The blood returned to the heart through systemic veins has less oxygen, since much of the oxygen carried by the arteries has been delivered to the cells. In contrast, in the pulmonary circuit, arteries carry blood low in oxygen exclusively to the lungs for gas exchange. Pulmonary veins then return freshly oxygenated blood from the lungs to the heart to be pumped back out into systemic circulation. Although arteries and veins differ structurally and functionally, they share certain features.
Anatomy

Figure 1. The pulmonary circuit moves blood from the right side of the heart to the lungs and back to the heart. The systemic circuit moves blood from the left side of the heart to the head and body and returns it to the right side of the heart to repeat the cycle. The arrows indicate the direction of blood flow, and the colors show the relative levels of oxygen concentration.

Shared Structures

Different types of blood vessels vary slightly in their structures, but they share the same general features. Arteries and arterioles have thicker walls than veins and venules because they are closer to the heart and receive blood that is surging at a far greater pressure (Figure 2). Each type of vessel has a lumen—a hollow passageway through which blood flows. Arteries have smaller lumens than veins, a characteristic that helps to maintain the pressure of blood moving through the system. Together, their thicker walls and smaller diameters give arterial lumens a more rounded appearance in cross section than the lumens of veins.
Figure 2. (a) Arteries and (b) veins share the same general features, but the walls of arteries are much thicker because of the higher pressure of the blood that flows through them. (c) A micrograph shows the relative differences in thickness. LM × 160. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

By the time blood has passed through capillaries and entered venules, the pressure initially exerted upon it by heart contractions has diminished. In other words, in comparison to arteries, venules and veins withstand a much lower pressure from the blood that flows through them. Their walls are considerably thinner and their lumens are correspondingly larger in diameter, allowing more blood to flow with less vessel resistance. In addition, many veins of the body, particularly those of the limbs, contain valves that assist the unidirectional flow of blood toward the heart. This is critical because blood flow becomes sluggish in the extremities, as a result of the lower pressure and the effects of gravity.

The walls of arteries and veins are largely composed of living cells and their products (including collagenous and elastic fibers); the cells require nourishment and produce waste. Since blood passes through the larger vessels relatively quickly, there is limited opportunity for blood in the lumen of the vessel to provide nourishment to or remove waste from the vessel’s cells. Further, the walls of the larger vessels are too thick for nutrients to diffuse through to all of the cells. Larger arteries and veins contain small blood vessels within their walls known as the vasa vasorum—literally “vessels of the vessel”—to provide them with this critical exchange. Since the pressure within arteries is relatively high, the vasa vasorum must function in the outer layers of the vessel or the pressure exerted by the blood passing through the vessel would collapse it, preventing any exchange from occurring. The
lower pressure within veins allows the vasa vasorum to be located closer to the lumen. The restriction of the vasa vasorum to the outer layers of arteries is thought to be one reason that arterial diseases are more common than venous diseases, since its location makes it more difficult to nourish the cells of the arteries and remove waste products. There are also minute nerves within the walls of both types of vessels that control the contraction and dilation of smooth muscle. These minute nerves are known as the nervi vasorum.

Both arteries and veins have the same three distinct tissue layers, called tunics (from the Latin term tunica), for the garments first worn by ancient Romans; the term tunic is also used for some modern garments. From the most interior layer to the outer, these tunics are the tunica intima, the tunica media, and the tunica externa. Table 1 compares and contrasts the tunics of the arteries and veins.

<table>
<thead>
<tr>
<th>Table 1. Comparison of Tunics in Arteries and Veins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arteries</strong></td>
</tr>
<tr>
<td><strong>General appearance</strong></td>
</tr>
<tr>
<td>Thick walls with small lumens; Generally appear rounded</td>
</tr>
<tr>
<td><strong>Tunica intima</strong></td>
</tr>
<tr>
<td>Endothelium usually appears wavy due to constriction of smooth muscle; Internal elastic membrane present in larger vessels</td>
</tr>
<tr>
<td><strong>Tunica media</strong></td>
</tr>
<tr>
<td>Normally the thickest layer in arteries; Smooth muscle cells and elastic fibers predominate (the proportions of these vary with distance from the heart); External elastic membrane present in larger vessels</td>
</tr>
<tr>
<td><strong>Tunica externa</strong></td>
</tr>
<tr>
<td>Normally thinner than the tunica media in all but the largest arteries; Collagenous and elastic fibers; Nervi vasorum and vasa vasorum present</td>
</tr>
</tbody>
</table>

**Tunica Intima**

The **tunica intima** (also called the tunica interna) is composed of epithelial and connective tissue layers. Lining the tunica intima is the specialized simple squamous epithelium called the endothelium, which is continuous throughout the entire vascular system, including the lining of the chambers of the heart. Damage to this endothelial lining and exposure of blood to the collagenous fibers beneath is one of the primary causes of clot formation. Until recently, the endothelium was viewed simply as the boundary between the blood in the lumen and the walls of the vessels. Recent studies, however, have shown that it is physiologically critical to such activities as helping to regulate capillary exchange and altering blood flow. The endothelium releases local chemicals called endothelins that can constrict the smooth muscle within the walls of the vessel to increase blood pressure. Uncompensated overproduction of endothelins may contribute to hypertension (high blood pressure) and cardiovascular disease.

Next to the endothelium is the basement membrane, or basal lamina, that effectively binds the endothelium to the connective tissue. The basement membrane provides strength while maintaining flexibility, and it is permeable, allowing materials to pass through it. The thin outer layer of the tunica intima contains a small amount of areolar connective tissue that consists primarily of elastic fibers to provide the vessel with additional flexibility; it also contains some collagenous fibers to provide additional strength.

In larger arteries, there is also a thick, distinct layer of elastic fibers known as the **internal elastic membrane** (also called the internal elastic lamina) at the boundary with the tunica media. Like the other components of the
tunica intima, the internal elastic membrane provides structure while allowing the vessel to stretch. It is permeated with small openings that allow exchange of materials between the tunics. The internal elastic membrane is not apparent in veins. In addition, many veins, particularly in the lower limbs, contain valves formed by sections of thickened endothelium that are reinforced with connective tissue, extending into the lumen.

Under the microscope, the lumen and the entire tunica intima of a vein will appear smooth, whereas those of an artery will normally appear wavy because of the partial constriction of the smooth muscle in the tunica media, the next layer of blood vessel walls.

**Tunica Media**

The **tunica media** is the substantial middle layer of the vessel wall (see Figure 2). It is generally the thickest layer in arteries, and it is much thicker in arteries than it is in veins. The tunica media consists of layers of smooth muscle supported by connective tissue that is primarily made up of elastic fibers, most of which are arranged in circular sheets. Toward the outer portion of the tunic, there are also layers of longitudinal muscle. Contraction and relaxation of the circular muscles decrease and increase the diameter of the vessel lumen, respectively. Specifically in arteries, **vasoconstriction** decreases blood flow as the smooth muscle in the walls of the tunica media contracts, making the lumen narrower and increasing blood pressure. Similarly, **vasodilation** increases blood flow as the smooth muscle relaxes, allowing the lumen to widen and blood pressure to drop. Both vasoconstriction and vasodilation are regulated in part by small vascular nerves, known as **nervi vasorum**, or “nerves of the vessel,” that run within the walls of blood vessels. These are generally all sympathetic fibers, although some trigger vasodilation and others induce vasoconstriction, depending upon the nature of the neurotransmitter and receptors located on the target cell. Parasympathetic stimulation does trigger vasodilation as well as erection during sexual arousal in the external genitalia of both sexes. Nervous control over vessels tends to be more generalized than the specific targeting of individual blood vessels. Local controls, discussed later, account for this phenomenon. (Seek additional content for more information on these dynamic aspects of the autonomic nervous system.) Hormones and local chemicals also control blood vessels. Together, these neural and chemical mechanisms reduce or increase blood flow in response to changing body conditions, from exercise to hydration. Regulation of both blood flow and blood pressure is discussed in detail later in this chapter.

The smooth muscle layers of the tunica media are supported by a framework of collagenous fibers that also binds the tunica media to the inner and outer tunics. Along with the collagenous fibers are large numbers of elastic fibers that appear as wavy lines in prepared slides. Separating the tunica media from the outer tunica externa in larger arteries is the **external elastic membrane** (also called the external elastic lamina), which also appears wavy in slides. This structure is not usually seen in smaller arteries, nor is it seen in veins.

**Tunica Externa**

The outer tunic, the **tunica externa** (also called the tunica adventitia), is a substantial sheath of connective tissue composed primarily of collagenous fibers. Some bands of elastic fibers are found here as well. The tunica externa in veins also contains groups of smooth muscle fibers. This is normally the thickest tunic in veins and may be thicker than the tunica media in some larger arteries. The outer layers of the tunica externa are not distinct but rather blend with the surrounding connective tissue outside the vessel, helping to hold the vessel in relative position. If you are able to palpate some of the superficial veins on your upper limbs and try to move them, you will find that the tunica externa prevents this. If the tunica externa did not hold the vessel in place, any movement would likely result in disruption of blood flow.

**Arteries**

An **artery** is a blood vessel that conducts blood away from the heart. All arteries have relatively thick walls that can withstand the high pressure of blood ejected from the heart. However, those close to the heart have the thickest walls, containing a high percentage of elastic fibers in all three of their tunics. This type of artery is known as an **elastic artery** (see Figure 3). Vessels larger than 10 mm in diameter are typically elastic. Their abundant elastic fibers allow them to expand, as blood pumped from the ventricles passes through them, and then to recoil after the surge has passed. If artery walls were rigid and unable to expand and recoil, their resistance to blood flow would greatly increase and blood pressure would rise to even higher levels, which would in turn require the heart to pump harder to increase the volume of blood expelled by each pump (the stroke volume) and maintain adequate pressure and flow. Artery walls would have to become even thicker in response to this
increased pressure. The elastic recoil of the vascular wall helps to maintain the pressure gradient that drives the blood through the arterial system. An elastic artery is also known as a conducting artery, because the large diameter of the lumen enables it to accept a large volume of blood from the heart and conduct it to smaller branches.

Farther from the heart, where the surge of blood has dampened, the percentage of elastic fibers in an artery’s tunica intima decreases and the amount of smooth muscle in its tunica media increases. The artery at this point is described as a **muscular artery**. The diameter of muscular arteries typically ranges from 0.1 mm to 10 mm. Their thick tunica media allows muscular arteries to play a leading role in vasoconstriction. In contrast, their decreased quantity of elastic fibers limits their ability to expand. Fortunately, because the blood pressure has eased by the time it reaches these more distant vessels, elasticity has become less important.

Notice that although the distinctions between elastic and muscular arteries are important, there is no “line of demarcation” where an elastic artery suddenly becomes muscular. Rather, there is a gradual transition as the vascular tree repeatedly branches. In turn, muscular arteries branch to distribute blood to the vast network of arterioles. For this reason, a muscular artery is also known as a distributing artery.

**Arterioles**

An **arteriole** is a very small artery that leads to a capillary. Arterioles have the same three tunics as the larger vessels, but the thickness of each is greatly diminished. The critical endothelial lining of the tunica intima is intact. The tunica media is restricted to one or two smooth muscle cell layers in thickness. The tunica externa remains but is very thin (see Figure 3).

With a lumen averaging 30 micrometers or less in diameter, arterioles are critical in slowing down—or resisting—blood flow and, thus, causing a substantial drop in blood pressure. Because of this, you may see them referred to as resistance vessels. The muscle fibers in arterioles are normally slightly contracted, causing arterioles to maintain a consistent muscle tone—in this case referred to as vascular tone—in a similar manner to the muscular tone of skeletal muscle. In reality, all blood vessels exhibit vascular tone due to the partial contraction of smooth muscle. The importance of the arterioles is that they will be the primary site of both resistance and regulation of blood pressure. The precise diameter of the lumen of an arteriole at any given moment is determined by neural and chemical controls, and vasoconstriction and vasodilation in the arterioles are the primary mechanisms for distribution of blood flow.

**Capillaries**

A **capillary** is a microscopic channel that supplies blood to the tissues themselves, a process called **perfusion**. Exchange of gases and other substances occurs in the capillaries between the blood and the surrounding cells and their tissue fluid (interstitial fluid). The diameter of a capillary lumen ranges from 5–10 micrometers; the smallest are just barely wide enough for an erythrocyte to squeeze through. Flow through capillaries is often described as
microcirculation.

The wall of a capillary consists of the endothelial layer surrounded by a basement membrane with occasional smooth muscle fibers. There is some variation in wall structure: In a large capillary, several endothelial cells bordering each other may line the lumen; in a small capillary, there may be only a single cell layer that wraps around to contact itself.

For capillaries to function, their walls must be leaky, allowing substances to pass through. There are three major types of capillaries, which differ according to their degree of “leakiness:” continuous, fenestrated, and sinusoid capillaries.

**Continuous Capillaries**

The most common type of capillary, the **continuous capillary**, is found in almost all vascularized tissues. Continuous capillaries are characterized by a complete endothelial lining with tight junctions between endothelial cells. Although a tight junction is usually impermeable and only allows for the passage of water and ions, they are often incomplete in capillaries, leaving intercellular clefts that allow for exchange of water and other very small molecules between the blood plasma and the interstitial fluid. Substances that can pass between cells include metabolic products, such as glucose, water, and small hydrophobic molecules like gases and hormones, as well as various leukocytes. Continuous capillaries not associated with the brain are rich in transport vesicles, contributing to either endocytosis or exocytosis. Those in the brain are part of the blood-brain barrier. Here, there are tight junctions and no intercellular clefts, plus a thick basement membrane and astrocyte extensions called end feet; these structures combine to prevent the movement of nearly all substances.

**Fenestrated Capillaries**

A **fenestrated capillary** is one that has pores (or fenestrations) in addition to tight junctions in the endothelial lining. These make the capillary permeable to larger molecules. The number of fenestrations and their degree of permeability vary, however, according to their location. Fenestrated capillaries are common in the small intestine, which is the primary site of nutrient absorption, as well as in the kidneys, which filter the blood. They are also found in the choroid plexus of the brain and many endocrine structures, including the hypothalamus, pituitary, pineal, and thyroid glands.

**Sinusoid Capillaries**

A **sinusoid capillary** (or sinusoid) is the least common type of capillary. Sinusoid capillaries are flattened, and they have extensive intercellular gaps and incomplete basement membranes, in addition to intercellular clefts and fenestrations. This gives them an appearance not unlike Swiss cheese. These very large openings allow for the passage of the largest molecules, including plasma proteins and even cells. Blood flow through sinusoids is very slow, allowing more time for exchange of gases, nutrients, and wastes. Sinusoids are found in the liver and spleen.
bone marrow, lymph nodes (where they carry lymph, not blood), and many endocrine glands including the pituitary and adrenal glands. Without these specialized capillaries, these organs would not be able to provide their myriad of functions. For example, when bone marrow forms new blood cells, the cells must enter the blood supply and can only do so through the large openings of a sinusoid capillary; they cannot pass through the small openings of continuous or fenestrated capillaries. The liver also requires extensive specialized sinusoid capillaries in order to process the materials brought to it by the hepatic portal vein from both the digestive tract and spleen, and to release plasma proteins into circulation.

**Metarterioles and Capillary Beds**

A metarteriole is a type of vessel that has structural characteristics of both an arteriole and a capillary. Slightly larger than the typical capillary, the smooth muscle of the tunica media of the metarteriole is not continuous but forms rings of smooth muscle (sphincters) prior to the entrance to the capillaries. Each metarteriole arises from a terminal arteriole and branches to supply blood to a capillary bed that may consist of 10–100 capillaries.

The precapillary sphincters, circular smooth muscle cells that surround the capillary at its origin with the metarteriole, tightly regulate the flow of blood from a metarteriole to the capillaries it supplies. Their function is critical: If all of the capillary beds in the body were to open simultaneously, they would collectively hold every drop of blood in the body and there would be none in the arteries, arterioles, venules, veins, or the heart itself. Normally, the precapillary sphincters are closed. When the surrounding tissues need oxygen and have excess waste products, the precapillary sphincters open, allowing blood to flow through and exchange to occur before closing once more (see Figure 5). If all of the precapillary sphincters in a capillary bed are closed, blood will flow from the metarteriole directly into a thoroughfare channel and then into the venous circulation, bypassing the capillary bed entirely. This creates what is known as a vascular shunt. In addition, an arteriovenous anastomosis may bypass the capillary bed and lead directly to the venous system.

Although you might expect blood flow through a capillary bed to be smooth, in reality, it moves with an irregular, pulsating flow. This pattern is called vasomotion and is regulated by chemical signals that are triggered in response to changes in internal conditions, such as oxygen, carbon dioxide, hydrogen ion, and lactic acid levels. For example, during strenuous exercise when oxygen levels decrease and carbon dioxide, hydrogen ion, and lactic acid levels all increase, the capillary beds in skeletal muscle are open, as they would be in the digestive system when nutrients are present in the digestive tract. During sleep or rest periods, vessels in both areas are largely closed; they open only occasionally to allow oxygen and nutrient supplies to travel to the tissues to maintain basic life processes.
Figure 5. In a capillary bed, arterioles give rise to metarterioles. Precapillary sphincters located at the junction of a metarteriole with a capillary regulate blood flow. A thoroughfare channel connects the metarteriole to a venule. An arteriovenous anastomosis, which directly connects the arteriole with the venule, is shown at the bottom.

Venules

A venule is an extremely small vein, generally 8–100 micrometers in diameter. Postcapillary venules join multiple capillaries exiting from a capillary bed. Multiple venules join to form veins. The walls of venules consist of endothelium, a thin middle layer with a few muscle cells and elastic fibers, plus an outer layer of connective tissue fibers that constitute a very thin tunica externa. Venules as well as capillaries are the primary sites of emigration or diapedesis, in which the white blood cells adhere to the endothelial lining of the vessels and then squeeze through adjacent cells to enter the tissue fluid.

Veins

A vein is a blood vessel that conducts blood toward the heart. Compared to arteries, veins are thin-walled vessels with large and irregular lumens (see Figure 6).
Figure 6. Many veins have valves to prevent back flow of blood, whereas venules do not. In terms of scale, the diameter of a venule is measured in micrometers compared to millimeters for veins.

Because they are low-pressure vessels, larger veins are commonly equipped with valves that promote the unidirectional flow of blood toward the heart and prevent backflow toward the capillaries caused by the inherent low blood pressure in veins as well as the pull of gravity. Table 2 compares the features of arteries and veins.

<table>
<thead>
<tr>
<th></th>
<th>Arteries</th>
<th>Veins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direction of blood flow</strong></td>
<td>Conducts blood away from the heart</td>
<td>Conducts blood toward the heart</td>
</tr>
<tr>
<td><strong>General appearance</strong></td>
<td>Rounded</td>
<td>Irregular, often collapsed</td>
</tr>
<tr>
<td><strong>Pressure</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Wall thickness</strong></td>
<td>Thick</td>
<td>Thin</td>
</tr>
<tr>
<td><strong>Relative oxygen concentration</strong></td>
<td>Higher in systemic arteries, Lower in pulmonary arteries</td>
<td>Lower in systemic veins, Higher in pulmonary veins</td>
</tr>
<tr>
<td><strong>Valves</strong></td>
<td>Not present</td>
<td>Present most commonly in limbs and in veins inferior to the heart</td>
</tr>
</tbody>
</table>
Disorders of the Cardiovascular System: Edema and Varicose Veins

Despite the presence of valves and the contributions of other anatomical and physiological adaptations we will cover shortly, over the course of a day, some blood will inevitably pool, especially in the lower limbs, due to the pull of gravity. Any blood that accumulates in a vein will increase the pressure within it, which can then be reflected back into the smaller veins, venules, and eventually even the capillaries. Increased pressure will promote the flow of fluids out of the capillaries and into the interstitial fluid. The presence of excess tissue fluid around the cells leads to a condition called edema.

Most people experience a daily accumulation of tissue fluid, especially if they spend much of their work life on their feet (like most health professionals). However, clinical edema goes beyond normal swelling and requires medical treatment. Edema has many potential causes, including hypertension and heart failure, severe protein deficiency, renal failure, and many others. In order to treat edema, which is a sign rather than a discrete disorder, the underlying cause must be diagnosed and alleviated.

Edema may be accompanied by varicose veins, especially in the superficial veins of the legs. This disorder arises when defective valves allow blood to accumulate within the veins, causing them to distend, twist, and become visible on the surface of the integument. Varicose veins may occur in both sexes, but are more common in women and are often related to pregnancy. More than simple cosmetic blemishes, varicose veins are often painful and sometimes itchy or throbbing. Without treatment, they tend to grow worse over time. The use of support hose, as well as elevating the feet and legs whenever possible, may be helpful in alleviating this condition. Laser surgery and interventional radiologic procedures can reduce the size and severity of varicose veins. Severe cases may require conventional surgery to remove the damaged vessels. As there are typically redundant circulation patterns, that is, anastomoses, for the smaller and more superficial veins, removal does not typically impair the circulation. There is evidence that patients with varicose veins suffer a greater risk of developing a thrombus or clot.

Figure 7. Varicose veins are commonly found in the lower limbs. (credit: Thomas Kriese)
Veins as Blood Reservoirs

In addition to their primary function of returning blood to the heart, veins may be considered blood reservoirs, since systemic veins contain approximately 64 percent of the blood volume at any given time. Their ability to hold this much blood is due to their high capacitance, that is, their capacity to distend (expand) readily to store a high volume of blood, even at a low pressure. The large lumens and relatively thin walls of veins make them far more distensible than arteries; thus, they are said to be capacitance vessels.

Summary: Distribution of Blood Flow

The following list breaks down the blood flow throughout the body:

- Systemic circulation 84%
  - Systemic veins 64%
    - Large veins 18%
    - Large venous networks (liver, bone marrow, and integument) 21%
    - Venules and medium sized veins 25%
  - Systemic arteries 13%
    - Arterioles 2%
    - Muscular arteries 5%
    - Elastic arteries 4%
    - Aorta 2%
    - Systemic capillaries 7%
- Pulmonary circulation 9%
  - Pulmonary veins 4%
  - Pulmonary arteries 3%
  - Pulmonary capillaries 2%
- Heart 7%

When blood flow needs to be redistributed to other portions of the body, the vasomotor center located in the medulla oblongata sends sympathetic stimulation to the smooth muscles in the walls of the veins, causing constriction—or in this case, venoconstriction. Less dramatic than the vasoconstriction seen in smaller arteries and arterioles, venoconstriction may be likened to a “stiffening” of the vessel wall. This increases pressure on the blood within the veins, speeding its return to the heart. As you will note in the image above, approximately 21 percent of the venous blood is located in venous networks within the liver, bone marrow, and integument. This volume of blood is referred to as venous reserve. Through venoconstriction, this “reserve” volume of blood can get back to the heart more quickly for redistribution to other parts of the circulation.

Careers in Action: Vascular Surgeons and Technicians

Vascular surgery is a specialty in which the physician deals primarily with diseases of the vascular portion of the cardiovascular system. This includes repair and replacement of diseased or damaged vessels, removal of plaque from vessels, minimally invasive procedures including the insertion of venous catheters, and traditional surgery. Following completion of medical school, the physician generally completes a 5-year surgical residency followed by an additional 1 to 2 years of vascular specialty training. In the United States, most vascular surgeons are members of the Society of Vascular Surgery.

Vascular technicians are specialists in imaging technologies that provide information on the health of the vascular system. They may also assist physicians in treating disorders involving the arteries and veins. This profession often overlaps with cardiovascular technology, which would also include treatments involving the heart. Although recognized by the American Medical Association, there are currently no licensing requirements for vascular technicians, and licensing is voluntary. Vascular technicians typically have an Associate’s degree or certificate, involving 18 months to 2 years of training. The United States Bureau of Labor projects this profession to grow by 29 percent from 2010 to 2020.
Chapter Review

Blood pumped by the heart flows through a series of vessels known as arteries, arterioles, capillaries, venules, and veins before returning to the heart. Arteries transport blood away from the heart and branch into smaller vessels, forming arterioles. Arterioles distribute blood to capillary beds, the sites of exchange with the body tissues. Capillaries lead back to small vessels known as venules that flow into the larger veins and eventually back to the heart.

The arterial system is a relatively high-pressure system, so arteries have thick walls that appear round in cross section. The venous system is a lower-pressure system, containing veins that have larger lumens and thinner walls. They often appear flattened. Arteries, arterioles, venules, and veins are composed of three tunics known as the tunica intima, tunica media, and tunica externa. Capillaries have only a tunica intima layer. The tunica intima is a thin layer composed of a simple squamous epithelium known as endothelium and a small amount of connective tissue. The tunica media is a thicker area composed of variable amounts of smooth muscle and connective tissue. It is the thickest layer in all but the largest arteries. The tunica externa is primarily a layer of connective tissue, although in veins, it also contains some smooth muscle. Blood flow through vessels can be dramatically influenced by vasoconstriction and vasodilation in their walls.

Critical Thinking Questions

Arterioles are often referred to as resistance vessels. Why?
Cocaine use causes vasoconstriction. Is this likely to increase or decrease blood pressure, and why?
A blood vessel with a few smooth muscle fibers and connective tissue, and only a very thin tunica externa conducts blood toward the heart. What type of vessel is this?

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Circulatory Pathways

Learning Objectives

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

- Identify the vessels through which blood travels within the pulmonary circuit, beginning from the right ventricle of the heart and ending at the left atrium
- Create a flow chart showing the major systemic arteries through which blood travels from the aorta and its major branches, to the most significant arteries feeding into the right and left upper and lower limbs
- Create a flow chart showing the major systemic veins through which blood travels from the feet to the right atrium of the heart

Virtually every cell, tissue, organ, and system in the body is impacted by the circulatory system. This includes the generalized and more specialized functions of transport of materials, capillary exchange, maintaining health by transporting white blood cells and various immunoglobulins (antibodies), hemostasis, regulation of body temperature, and helping to maintain acid-base balance. In addition to these shared functions, many systems enjoy a unique relationship with the circulatory system. Table 1 summarizes these relationships.

<table>
<thead>
<tr>
<th>System</th>
<th>Diagram</th>
<th>Roles of Circulatory System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive</td>
<td></td>
<td>Absorbs nutrients and water; delivers nutrients (except most lipids) to liver for processing by hepatic portal vein; provides nutrients essential for hematopoiesis and building hemoglobin</td>
</tr>
<tr>
<td>Endocrine</td>
<td><img src="image" alt="Diagram" /></td>
<td>Delivers hormones: atrial natriuretic hormone (peptide) secreted by the heart atrial cells to help regulate blood volumes and pressures; epinephrine, ANH, angiotensin II, ADH, and thyroxine to help regulate blood pressure; estrogen to promote vascular health in women and men</td>
</tr>
<tr>
<td>Integumentary</td>
<td><img src="image" alt="Diagram" /></td>
<td>Carries clotting factors, platelets, and white blood cells for homeostasis, fighting infection, and repairing damage; regulates temperature by controlling blood flow to the surface, where heat can be dissipated; provides some coloration of integument; acts as a blood reservoir</td>
</tr>
<tr>
<td>Table 1. Interaction of the Circulatory System with Other Body Systems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lymphatic</strong></td>
<td>Transports various white blood cells, including those produced by lymphatic tissue, and immunoglobulins (antibodies) throughout the body to maintain health; carries excess tissue fluid not able to be reabsorbed by the vascular capillaries back to the lymphatic system for processing</td>
<td></td>
</tr>
<tr>
<td><strong>Muscular</strong></td>
<td>Provides nutrients and oxygen for contraction; removes lactic acid and distributes heat generated by contraction; muscular pumps aid in venous return; exercise contributes to cardiovascular health and helps to prevent atherosclerosis</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous</strong></td>
<td>Produces cerebrospinal fluid (CSF) within choroid plexuses; contributes to blood–brain barrier; cardiac and vasomotor centers regulate cardiac output and blood flow through vessels via autonomic system</td>
<td></td>
</tr>
<tr>
<td><strong>Reproductive</strong></td>
<td>Aids in erection of genetalia during sexual arousal; transports gonadotropic hormones that regulate reproductive functions</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td>Provides blood for critical exchange of gases to carry oxygen needed for metabolic reactions and carbon dioxide generated as byproducts of these processes</td>
<td></td>
</tr>
<tr>
<td><strong>Skeletal</strong></td>
<td>Provides calcium, phosphate, and other minerals critical for bone matrix; transports hormones regulating buildup and absorption of matrix including growth hormone (somatotropin), thyroid hormone, calcitonins, and parathyroid hormone; erythropoietin stimulates myeloid cell hematopoiesis; some level of protection for select vessels by bony structures</td>
<td></td>
</tr>
<tr>
<td><strong>Urinary</strong></td>
<td>Delivers 20 percent of resting circulation to kidneys for filtering, reabsorption of useful products, and secretion of excesses; regulates blood volume and pressure by regulating fluid loss in the form of urine and by releasing the enzyme renin that is essential in the renin-angiotensin-aldosterone mechanism</td>
<td></td>
</tr>
</tbody>
</table>

As you learn about the vessels of the systemic and pulmonary circuits, notice that many arteries and veins share the same names, parallel one another throughout the body, and are very similar on the right and left sides of the body. These pairs of vessels will be traced through only one side of the body. Where differences occur in branching patterns or when vessels are singular, this will be indicated. For example, you will find a pair of femoral
arteries and a pair of femoral veins, with one vessel on each side of the body. In contrast, some vessels closer to the midline of the body, such as the aorta, are unique. Moreover, some superficial veins, such as the great saphenous vein in the femoral region, have no arterial counterpart.

Another phenomenon that can make the study of vessels challenging is that names of vessels can change with location. Like a street that changes name as it passes through an intersection, an artery or vein can change names as it passes an anatomical landmark. For example, the left subclavian artery becomes the axillary artery as it passes through the body wall and into the axillary region, and then becomes the brachial artery as it flows from the axillary region into the upper arm (or brachium). You will also find examples of anastomoses where two blood vessels that previously branched reconnect. Anastomoses are especially common in veins, where they help maintain blood flow even when one vessel is blocked or narrowed, although there are some important ones in the arteries supplying the brain.

As you read about circular pathways, notice that there is an occasional, very large artery referred to as a trunk, a term indicating that the vessel gives rise to several smaller arteries. For example, the celiac trunk gives rise to the left gastric, common hepatic, and splenic arteries.

As you study this section, imagine you are on a “Voyage of Discovery” similar to Lewis and Clark’s expedition in 1804–1806, which followed rivers and streams through unfamiliar territory, seeking a water route from the Atlantic to the Pacific Ocean. You might envision being inside a miniature boat, exploring the various branches of the circulatory system. This simple approach has proven effective for many students in mastering these major circulatory patterns. Another approach that works well for many students is to create simple line drawings similar to the ones provided, labeling each of the major vessels. It is beyond the scope of this text to name every vessel in the body. However, we will attempt to discuss the major pathways for blood and acquaint you with the major named arteries and veins in the body. Also, please keep in mind that individual variations in circulation patterns are not uncommon.

### Pulmonary Circulation

Recall that blood returning from the systemic circuit enters the right atrium via the superior and inferior venae cavae and the coronary sinus, which drains the blood supply of the heart muscle. These vessels will be described more fully later in this section. This blood is relatively low in oxygen and relatively high in carbon dioxide, since much of the oxygen has been extracted for use by the tissues and the waste gas carbon dioxide was picked up to be transported to the lungs for elimination. From the right atrium, blood moves into the right ventricle, which pumps it to the lungs for gas exchange. This system of vessels is referred to as the pulmonary circuit.

The single vessel exiting the right ventricle is the pulmonary trunk. At the base of the pulmonary trunk is the pulmonary semilunar valve, which prevents backflow of blood into the right ventricle during ventricular diastole. As the pulmonary trunk reaches the superior surface of the heart, it curves posteriorly and rapidly bifurcates (divides) into two branches, a left and a right pulmonary artery. To prevent confusion between these vessels, it is important to refer to the vessel exiting the heart as the pulmonary trunk, rather than also calling it a pulmonary artery. The pulmonary arteries in turn branch many times within the lung, forming a series of smaller arteries and arterioles that eventually lead to the pulmonary capillaries. The pulmonary capillaries surround lung structures known as alveoli that are the sites of oxygen and carbon dioxide exchange.

Once gas exchange is completed, oxygenated blood flows from the pulmonary capillaries into a series of pulmonary venules that eventually lead to a series of larger pulmonary veins. Four pulmonary veins, two on the left and two on the right, return blood to the left atrium. At this point, the pulmonary circuit is complete. The image, and table below defines the major arteries and veins of the pulmonary circuit discussed in the text.
Figure 1. Blood exiting from the right ventricle flows into the pulmonary trunk, which bifurcates into the two pulmonary arteries. These vessels branch to supply blood to the pulmonary capillaries, where gas exchange occurs within the lung alveoli. Blood returns via the pulmonary veins to the left atrium.

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary trunk</td>
<td>Single large vessel exiting the right ventricle that divides to form the right and left pulmonary arteries</td>
</tr>
<tr>
<td>Pulmonary arteries</td>
<td>Left and right vessels that form from the pulmonary trunk and lead to smaller arterioles and eventually to the pulmonary capillaries</td>
</tr>
<tr>
<td>Pulmonary veins</td>
<td>Two sets of paired vessels—one pair on each side—that are formed from the small venules, leading away from the pulmonary capillaries to flow into the left atrium</td>
</tr>
</tbody>
</table>

Overview of Systemic Arteries

Blood relatively high in oxygen concentration is returned from the pulmonary circuit to the left atrium via the four pulmonary veins. From the left atrium, blood moves into the left ventricle, which pumps blood into the aorta. The aorta and its branches—the systemic arteries—send blood to virtually every organ of the body.
The Aorta

The aorta is the largest artery in the body. It arises from the left ventricle and eventually descends to the abdominal region, where it bifurcates at the level of the fourth lumbar vertebra into the two common iliac arteries. The aorta consists of the ascending aorta, the aortic arch, and the descending aorta, which passes through the diaphragm and a landmark that divides into the superior thoracic and inferior abdominal components. Arteries originating from the aorta ultimately distribute blood to virtually all tissues of the body. At the base of the aorta is the aortic semilunar valve that prevents backflow of blood into the left ventricle while the heart is relaxing. After exiting the heart, the ascending aorta moves in a superior direction for approximately 5 cm and ends at the sternal angle. Following this ascent, it reverses direction, forming a graceful arc to the left, called the aortic arch. The aortic arch descends toward the inferior portions of the body and ends at the level of the intervertebral disk between the fourth and fifth thoracic vertebrae. Beyond this point, the descending aorta continues close to the bodies of the vertebrae and passes through an opening in the diaphragm known as the aortic hiatus. Superior to the diaphragm, the aorta is called the thoracic aorta, and inferior to the diaphragm, it is called the
**abdominal aorta.** The abdominal aorta terminates when it bifurcates into the two common iliac arteries at the level of the fourth lumbar vertebra. See Figure 3 for an illustration of the ascending aorta, the aortic arch, and the initial segment of the descending aorta plus major branches; Table 3 summarizes the structures of the aorta.

![Diagram of the aorta](image)

*Figure 3. The aorta has distinct regions, including the ascending aorta, aortic arch, and the descending aorta, which includes the thoracic and abdominal regions.*

<table>
<thead>
<tr>
<th><strong>Table 3. Components of the Aorta</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vessel</strong></td>
</tr>
<tr>
<td>Aorta</td>
</tr>
<tr>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>Largest artery in the body, originating from the left ventricle and descending to the abdominal region, where it bifurcates into the common iliac arteries at the level of the fourth lumbar vertebra; arteries originating from the aorta distribute blood to virtually all tissues of the body</td>
</tr>
<tr>
<td>Ascending aorta</td>
</tr>
<tr>
<td>Initial portion of the aorta, rising superiorly from the left ventricle for a distance of approximately 5 cm</td>
</tr>
<tr>
<td>Aortic arch</td>
</tr>
<tr>
<td>Graceful arc to the left that connects the ascending aorta to the descending aorta; ends at the intervertebral disk between the fourth and fifth thoracic vertebrae</td>
</tr>
<tr>
<td>Descending aorta</td>
</tr>
<tr>
<td>Portion of the aorta that continues inferiorly past the end of the aortic arch; subdivided into the thoracic aorta and the abdominal aorta</td>
</tr>
<tr>
<td>Thoracic aorta</td>
</tr>
<tr>
<td>Portion of the descending aorta superior to the aortic hiatus</td>
</tr>
<tr>
<td>Abdominal aorta</td>
</tr>
<tr>
<td>Portion of the aorta inferior to the aortic hiatus and superior to the common iliac arteries</td>
</tr>
</tbody>
</table>
Coronary Circulation

The first vessels that branch from the ascending aorta are the paired coronary arteries, which arise from two of the three sinuses in the ascending aorta just superior to the aortic semilunar valve. These sinuses contain the aortic baroreceptors and chemoreceptors critical to maintain cardiac function. The left coronary artery arises from the left posterior aortic sinus. The right coronary artery arises from the anterior aortic sinus. Normally, the right posterior aortic sinus does not give rise to a vessel.

The coronary arteries encircle the heart, forming a ring-like structure that divides into the next level of branches that supplies blood to the heart tissues. (Seek additional content for more detail on cardiac circulation.)

Aortic Arch Branches

There are three major branches of the aortic arch: the brachiocephalic artery, the left common carotid artery, and the left subclavian (literally “under the clavicle”) artery. As you would expect based upon proximity to the heart, each of these vessels is classified as an elastic artery.

The brachiocephalic artery is located only on the right side of the body; there is no corresponding artery on the left. The brachiocephalic artery branches into the right subclavian artery and the right common carotid artery. The left subclavian and left common carotid arteries arise independently from the aortic arch but otherwise follow a similar pattern and distribution to the corresponding arteries on the right side (see Figure 2).

Each subclavian artery supplies blood to the arms, chest, shoulders, back, and central nervous system. It then gives rise to three major branches: the internal thoracic artery, the vertebral artery, and the thyrocervical artery. The internal thoracic artery, or mammary artery, supplies blood to the thymus, the pericardium of the heart, and the anterior chest wall. The vertebral artery passes through the vertebral foramen in the cervical vertebrae and then through the foramen magnum into the cranial cavity to supply blood to the brain and spinal cord. The paired vertebral arteries join together to form the large basilar artery at the base of the medulla oblongata. This is an example of an anastomosis. The subclavian artery also gives rise to the thyrocervical artery that provides blood to the thyroid, the cervical region of the neck, and the upper back and shoulder.

The common carotid artery divides into internal and external carotid arteries. The right common carotid artery arises from the brachiocephalic artery and the left common carotid artery arises directly from the aortic arch. The external carotid artery supplies blood to numerous structures within the face, lower jaw, neck, esophagus, and larynx. These branches include the lingual, facial, occipital, maxillary, and superficial temporal arteries. The internal carotid artery initially forms an expansion known as the carotid sinus, containing the carotid baroreceptors and chemoreceptors. Like their counterparts in the aortic sinuses, the information provided by these receptors is critical to maintaining cardiovascular homeostasis (see Figure 2).

The internal carotid arteries along with the vertebral arteries are the two primary suppliers of blood to the human brain. Given the central role and vital importance of the brain to life, it is critical that blood supply to this organ remains uninterrupted. Recall that blood flow to the brain is remarkably constant, with approximately 20 percent of blood flow directed to this organ at any given time. When blood flow is interrupted, even for just a few seconds, a transient ischemic attack (TIA), or mini-stroke, may occur, resulting in loss of consciousness or temporary loss of neurological function. In some cases, the damage may be permanent. Loss of blood flow for longer periods, typically between 3 and 4 minutes, will likely produce irreversible brain damage or a stroke, also called a cerebrovascular accident (CVA). The locations of the arteries in the brain not only provide blood flow to the brain tissue but also prevent interruption in the flow of blood. Both the carotid and vertebral arteries branch once they enter the cranial cavity, and some of these branches form a structure known as the arterial circle (or circle of Willis), an anastomosis that is remarkably like a traffic circle that sends off branches (in this case, arterial branches to the brain). As a rule, branches to the anterior portion of the cerebrum are normally fed by the internal carotid arteries; the remainder of the brain receives blood flow from branches associated with the vertebral...
The internal carotid artery continues through the carotid canal of the temporal bone and enters the base of the brain through the carotid foramen where it gives rise to several branches (see Figure 4 and Figure 5).

One of these branches is the **anterior cerebral artery** that supplies blood to the frontal lobe of the cerebrum. Another branch, the **middle cerebral artery**, supplies blood to the temporal and parietal lobes, which are the most common sites of CVAs. The **ophthalmic artery**, the third major branch, provides blood to the eyes.

The right and left anterior cerebral arteries join together to form an anastomosis called the **anterior communicating artery**. The initial segments of the anterior cerebral arteries and the anterior communicating artery form the anterior portion of the arterial circle. The posterior portion of the arterial circle is formed by a left and a right **posterior communicating artery** that branches from the **posterior cerebral artery**, which arises from the basilar artery. It provides blood to the posterior portion of the cerebrum and brain stem. The **basilar artery** is an anastomosis that begins at the junction of the two vertebral arteries and sends branches to the cerebellum and brain stem. It flows into the posterior cerebral arteries. Table 4 summarizes the aortic arch branches, including the major branches supplying the brain.

![Figure 4. The common carotid artery gives rise to the external and internal carotid arteries. The external carotid artery remains superficial and gives rise to many arteries of the head. The internal carotid artery first forms the carotid sinus and then reaches the brain via the carotid canal and carotid foramen, emerging into the cranium via the foramen lacerum. The vertebral artery branches from the subclavian artery and passes through the transverse foramen in the cervical vertebrae, entering the base of the skull at the vertebral foramen. The subclavian artery continues toward the arm as the axillary artery.](image-url)
Figure 5. This inferior view shows the network of arteries serving the brain. The structure is referred to as the arterial circle or circle of Willis.

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachiocephalic artery</td>
<td>Single vessel located on the right side of the body; the first vessel branching from the aortic arch; gives rise to the right subclavian artery and the right common carotid artery; supplies blood to the head, neck, upper limb, and wall of the thoracic region</td>
</tr>
<tr>
<td>Subclavian artery</td>
<td>The right subclavian artery arises from the brachiocephalic artery while the left subclavian artery arises from the aortic arch; gives rise to the internal thoracic, vertebral, and thyrocervical arteries; supplies blood to the arms, chest, shoulders, back, and central nervous system</td>
</tr>
<tr>
<td>Internal thoracic artery</td>
<td>Also called the mammary artery; arises from the subclavian artery; supplies blood to the thymus, pericardium of the heart, and anterior chest wall</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>Arises from the subclavian artery and passes through the vertebral foramen through the foramen magnum to the brain; joins with the internal carotid artery to form the arterial circle; supplies blood to the brain and spinal cord</td>
</tr>
<tr>
<td>Thyrocervical artery</td>
<td>Arises from the subclavian artery; supplies blood to the thyroid, the cervical region, the upper back, and shoulder</td>
</tr>
<tr>
<td>Common carotid artery</td>
<td>The right common carotid artery arises from the brachiocephalic artery and the left common carotid artery arises from the aortic arch; each gives rise to the external and internal carotid arteries; supplies the respective sides of the head and neck</td>
</tr>
</tbody>
</table>
### Table 4. Aortic Arch Branches and Brain Circulation

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>External carotid artery</td>
<td>Arises from the common carotid artery; supplies blood to numerous structures within the face, lower jaw, neck, esophagus, and larynx</td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>Arises from the common carotid artery and begins with the carotid sinus; goes through the carotid canal of the temporal bone to the base of the brain; combines with the branches of the vertebral artery, forming the arterial circle; supplies blood to the brain</td>
</tr>
<tr>
<td>Arterial circle or circle of Willis</td>
<td>An anastomosis located at the base of the brain that ensures continual blood supply; formed from the branches of the internal carotid and vertebral arteries; supplies blood to the brain</td>
</tr>
<tr>
<td>Anterior cerebral artery</td>
<td>Arises from the internal carotid artery; supplies blood to the frontal lobe of the cerebrum</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>Another branch of the internal carotid artery; supplies blood to the temporal and parietal lobes of the cerebrum</td>
</tr>
<tr>
<td>Ophthalmic artery</td>
<td>Branch of the internal carotid artery; supplies blood to the eyes</td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>An anastomosis of the right and left internal carotid arteries; supplies blood to the brain</td>
</tr>
<tr>
<td>Posterior communicating artery</td>
<td>Branches of the posterior cerebral artery that form part of the posterior portion of the arterial circle; supplies blood to the brain</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>Branch of the basilar artery that forms a portion of the posterior segment of the arterial circle of Willis; supplies blood to the posterior portion of the cerebrum and brain stem</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>Formed from the fusion of the two vertebral arteries; sends branches to the cerebellum, brain stem, and the posterior cerebral arteries; the main blood supply to the brain stem</td>
</tr>
</tbody>
</table>

### Thoracic Aorta and Major Branches

The thoracic aorta begins at the level of vertebra T5 and continues through to the diaphragm at the level of T12, initially traveling within the mediastinum to the left of the vertebral column. As it passes through the thoracic region, the thoracic aorta gives rise to several branches, which are collectively referred to as visceral branches and parietal branches. Those branches that supply blood primarily to visceral organs are known as the **visceral branches** and include the bronchial arteries, pericardial arteries, esophageal arteries, and the mediastinal arteries, each named after the tissues it supplies. Each **bronchial artery** (typically two on the left and one on the right) supplies systemic blood to the lungs and visceral pleura, in addition to the blood pumped to the lungs for oxygenation via the pulmonary circuit. The bronchial arteries follow the same path as the respiratory branches, beginning with the bronchi and ending with the bronchioles. There is considerable, but not total, intermingling of the systemic and pulmonary blood at anastomoses in the smaller branches of the lungs. This may sound incongruous—that is, the mixing of systemic arterial blood high in oxygen with the pulmonary arterial blood lower
in oxygen—but the systemic vessels also deliver nutrients to the lung tissue just as they do elsewhere in the body. The mixed blood drains into typical pulmonary veins, whereas the bronchial artery branches remain separate and drain into bronchial veins described later. Each pericardial artery supplies blood to the pericardium, the esophageal artery provides blood to the esophagus, and the mediastinal artery provides blood to the mediastinum. The remaining thoracic aorta branches are collectively referred to as parietal branches or somatic branches, and include the intercostal and superior phrenic arteries. Each intercostal artery provides blood to the muscles of the thoracic cavity and vertebral column. The superior phrenic artery provides blood to the superior surface of the diaphragm. The image and table below lists the arteries of the thoracic region.

---

**Table 5. Arteries of the Thoracic Region**

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral branches</td>
<td>A group of arterial branches of the thoracic aorta; supplies blood to the viscera (i.e., organs) of the thorax</td>
</tr>
<tr>
<td>Bronchial artery</td>
<td>Systemic branch from the aorta that provides oxygenated blood to the lungs; this blood supply is in addition to the pulmonary circuit that brings blood for oxygenation</td>
</tr>
<tr>
<td>Pericardial artery</td>
<td>Branch of the thoracic aorta; supplies blood to the pericardium</td>
</tr>
<tr>
<td>Esophageal artery</td>
<td>Branch of the thoracic aorta; supplies blood to the esophagus</td>
</tr>
</tbody>
</table>

---

*Figure 6. The thoracic aorta gives rise to the arteries of the visceral and parietal branches.*
Table 5. Arteries of the Thoracic Region

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinal artery</td>
<td>Branch of the thoracic aorta; supplies blood to the mediastinum</td>
</tr>
<tr>
<td>Parietal branches</td>
<td>Also called somatic branches, a group of arterial branches of the thoracic aorta; include those that supply blood to the thoracic wall, vertebral column, and the superior surface of the diaphragm</td>
</tr>
<tr>
<td>Intercostal artery</td>
<td>Branch of the thoracic aorta; supplies blood to the muscles of the thoracic cavity and vertebral column</td>
</tr>
<tr>
<td>Superior phrenic artery</td>
<td>Branch of the thoracic aorta; supplies blood to the superior surface of the diaphragm</td>
</tr>
</tbody>
</table>

Abdominal Aorta and Major Branches

After crossing through the diaphragm at the aortic hiatus, the thoracic aorta is called the abdominal aorta (Figure 6). This vessel remains to the left of the vertebral column and is embedded in adipose tissue behind the peritoneal cavity. It formally ends at approximately the level of vertebra L4, where it bifurcates to form the common iliac arteries. Before this division, the abdominal aorta gives rise to several important branches. A single celiac trunk (artery) emerges and divides into the left gastric artery to supply blood to the stomach and esophagus, the splenic artery to supply blood to the spleen, and the common hepatic artery, which in turn gives rise to the hepatic artery proper to supply blood to the liver, the right gastric artery to supply blood to the stomach, the cystic artery to supply blood to the gall bladder, and several branches, one to supply blood to the duodenum and another to supply blood to the pancreas. Two additional single vessels arise from the abdominal aorta. These are the superior and inferior mesenteric arteries. The superior mesenteric artery arises approximately 2.5 cm after the celiac trunk and branches into several major vessels that supply blood to the small intestine (duodenum, jejunum, and ileum), the pancreas, and a majority of the large intestine. The inferior mesenteric artery supplies blood to the distal segment of the large intestine, including the rectum. It arises approximately 5 cm superior to the common iliac arteries.

In addition to these single branches, the abdominal aorta gives rise to several significant paired arteries along the way. These include the inferior phrenic arteries, the adrenal arteries, the renal arteries, the gonadal arteries, and the lumbar arteries. Each inferior phrenic artery is a counterpart of a superior phrenic artery and supplies blood to the inferior surface of the diaphragm. The adrenal artery supplies blood to the adrenal (suprarenal) glands and arises near the superior mesenteric artery. Each renal artery branches approximately 2.5 cm inferior to the superior mesenteric arteries and supplies a kidney. The right renal artery is longer than the left since the aorta lies to the left of the vertebral column and the vessel must travel a greater distance to reach its target. Renal arteries branch repeatedly to supply blood to the kidneys. Each gonadal artery supplies blood to the gonads, or reproductive organs, and is also described as either an ovarian artery or a testicular artery (internal spermatic), depending upon the sex of the individual. An ovarian artery supplies blood to an ovary, uterine (Fallopian) tube, and the uterus, and is located within the suspensory ligament of the uterus. It is considerably shorter than a testicular artery, which ultimately travels outside the body cavity to the testes, forming one component of the spermatic cord. The gonadal arteries arise inferior to the renal arteries and are generally retroperitoneal. The ovarian artery continues to the uterus where it forms an anastomosis with the uterine artery that supplies blood to the uterus. Both the uterine arteries and vaginal arteries, which distribute blood to the vagina, are branches of the internal iliac artery. The four paired lumbar arteries are the counterparts of the intercostal arteries and supply blood to the lumbar region, the abdominal wall, and the spinal cord. In some instances, a fifth pair of lumbar arteries emerges from the median sacral artery.

The aorta divides at approximately the level of vertebra L4 into a left and a right common iliac artery but continues as a small vessel, the median sacral artery, into the sacrum. The common iliac arteries provide blood to the pelvic region and ultimately to the lower limbs. They split into external and internal iliac arteries approximately at the level of the lumbar-sacral articulation. Each internal iliac artery sends branches to the
Anatomy

urinary bladder, the walls of the pelvis, the external genitalia, and the medial portion of the femoral region. In females, they also provide blood to the uterus and vagina. The much larger external iliac artery supplies blood to each of the lower limbs. Figure 8 shows the distribution of the major branches of the aorta into the thoracic and abdominal regions. Figure 9 shows the distribution of the major branches of the common iliac arteries.

**Figure 7.** The flow chart summarizes the distribution of the major branches of the aorta into the thoracic and abdominal regions.
Figure 8. The flow chart below summarizes the distribution of the major branches of the common iliac arteries into the pelvis and lower limbs. The left side follows a similar pattern to the right.

Table 6 summarizes the major branches of the abdominal aorta.

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac trunk</td>
<td>Also called the celiac artery; a major branch of the abdominal aorta; gives rise to the left gastric artery, the splenic artery, and the common hepatic artery that forms the hepatic artery to the liver, the right gastric artery to the stomach, and the cystic artery to the gall bladder</td>
</tr>
<tr>
<td>Left gastric artery</td>
<td>Branch of the celiac trunk; supplies blood to the stomach</td>
</tr>
<tr>
<td>Splenic artery</td>
<td>Branch of the celiac trunk; supplies blood to the spleen</td>
</tr>
<tr>
<td>Common hepatic artery</td>
<td>Branch of the celiac trunk that forms the hepatic artery, the right gastric artery, and the cystic artery</td>
</tr>
<tr>
<td>Hepatic artery proper</td>
<td>Branch of the common hepatic artery; supplies systemic blood to the liver</td>
</tr>
<tr>
<td>Right gastric artery</td>
<td>Branch of the common hepatic artery; supplies blood to the stomach</td>
</tr>
<tr>
<td>Cystic artery</td>
<td>Branch of the common hepatic artery; supplies blood to the gall bladder</td>
</tr>
</tbody>
</table>
### Table 6. Vessels of the Abdominal Aorta

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior mesenteric artery</td>
<td>Branch of the abdominal aorta; supplies blood to the small intestine (duodenum, jejunum, and ileum), the pancreas, and a majority of the large intestine</td>
</tr>
<tr>
<td>Inferior mesenteric artery</td>
<td>Branch of the abdominal aorta; supplies blood to the distal segment of the large intestine and rectum</td>
</tr>
<tr>
<td>Inferior phrenic arteries</td>
<td>Branches of the abdominal aorta; supply blood to the inferior surface of the diaphragm</td>
</tr>
<tr>
<td>Adrenal artery</td>
<td>Branch of the abdominal aorta; supplies blood to the adrenal (suprarenal) glands</td>
</tr>
<tr>
<td>Renal artery</td>
<td>Branch of the abdominal aorta; supplies each kidney</td>
</tr>
<tr>
<td>Gonadal artery</td>
<td>Branch of the abdominal aorta; supplies blood to the gonads or reproductive organs; also described as ovarian arteries or testicular arteries, depending upon the sex of the individual</td>
</tr>
<tr>
<td>Ovarian artery</td>
<td>Branch of the abdominal aorta; supplies blood to ovary, uterine (Fallopian) tube, and uterus</td>
</tr>
<tr>
<td>Testicular artery</td>
<td>Branch of the abdominal aorta; ultimately travels outside the body cavity to the testes and forms one component of the spermatic cord</td>
</tr>
<tr>
<td>Lumbar arteries</td>
<td>Branches of the abdominal aorta; supply blood to the lumbar region, the abdominal wall, and spinal cord</td>
</tr>
<tr>
<td>Common iliac artery</td>
<td>Branch of the aorta that leads to the internal and external iliac arteries</td>
</tr>
<tr>
<td>Median sacral artery</td>
<td>Continuation of the aorta into the sacrum</td>
</tr>
<tr>
<td>Internal iliac artery</td>
<td>Branch from the common iliac arteries; supplies blood to the urinary bladder, walls of the pelvis, external genitalia, and the medial portion of the femoral region; in females, also provides blood to the uterus and vagina</td>
</tr>
<tr>
<td>External iliac artery</td>
<td>Branch of the common iliac artery that leaves the body cavity and becomes a femoral artery; supplies blood to the lower limbs</td>
</tr>
</tbody>
</table>

**Arteries Serving the Upper Limbs**
As the subclavian artery exits the thorax into the axillary region, it is renamed the axillary artery. Although it does branch and supply blood to the region near the head of the humerus (via the humeral circumflex arteries), the majority of the vessel continues into the upper arm, or brachium, and becomes the brachial artery (Figure 9).

The brachial artery supplies blood to much of the brachial region and divides at the elbow into several smaller branches, including the deep brachial arteries, which provide blood to the posterior surface of the arm, and the ulnar collateral arteries, which supply blood to the region of the elbow.

As the brachial artery approaches the coronoid fossa, it bifurcates into the radial and ulnar arteries, which continue into the forearm, or antebrachium. The radial artery and ulnar artery parallel their namesake bones, giving off smaller branches until they reach the wrist, or carpal region. At this level, they fuse to form the superficial and deep palmar arches that supply blood to the hand, as well as the digital arteries that supply blood to the digits. Figure 9 show the distribution of systemic arteries from the heart into the upper limb. Table 7 summarizes the arteries serving the upper limbs.

Figure 9. The arteries that supply blood to the arms and hands are extensions of the subclavian arteries.
Figure 10. The flow chart summarizes the distribution of the major arteries from the heart into the upper limb.

Table 7. Arteries Serving the Upper Limbs

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary artery</td>
<td>Continuation of the subclavian artery as it penetrates the body wall and enters the axillary region; supplies blood to the region near the head of the humerus (humeral circumflex arteries); the majority of the vessel continues into the brachium and becomes the brachial artery</td>
</tr>
<tr>
<td>Brachial artery</td>
<td>Continuation of the axillary artery in the brachium; supplies blood to much of the brachial region; gives off several smaller branches that provide blood to the posterior surface of the arm in the region of the elbow; bifurcates into the radial and ulnar arteries at the coronoid fossa</td>
</tr>
<tr>
<td>Radial artery</td>
<td>Formed at the bifurcation of the brachial artery; parallels the radius; gives off smaller branches until it reaches the carpal region where it fuses with the ulnar artery to form the superficial and deep palmar arches; supplies blood to the lower arm and carpal region</td>
</tr>
</tbody>
</table>
Table 7. Arteries Serving the Upper Limbs

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulnar artery</td>
<td>Formed at the bifurcation of the brachial artery; parallels the ulna; gives off smaller branches until it reaches the carpal region where it fuses with the radial artery to form the superficial and deep palmar arches; supplies blood to the lower arm and carpal region</td>
</tr>
<tr>
<td>Palmar arches (superficial and deep)</td>
<td>Formed from anastomosis of the radial and ulnar arteries; supply blood to the hand and digital arteries</td>
</tr>
<tr>
<td>Digital arteries</td>
<td>Formed from the superficial and deep palmar arches; supply blood to the digits</td>
</tr>
</tbody>
</table>

Arteries Serving the Lower Limbs

The external iliac artery exits the body cavity and enters the femoral region of the lower leg (Figure 11). As it passes through the body wall, it is renamed the **femoral artery**. It gives off several smaller branches as well as the lateral **deep femoral artery** that in turn gives rise to a **lateral circumflex artery**. These arteries supply blood to the deep muscles of the thigh as well as ventral and lateral regions of the integument. The femoral artery also gives rise to the **genicular artery**, which provides blood to the region of the knee. As the femoral artery passes posterior to the knee near the popliteal fossa, it is called the popliteal artery. The **popliteal artery** branches into the anterior and posterior tibial arteries.

![Figure 11. Major arteries serving the lower limb are shown in anterior and posterior views.](image-url)
Anatomy

The anterior tibial artery is located between the tibia and fibula, and supplies blood to the muscles and integument of the anterior tibial region. Upon reaching the tarsal region, it becomes the dorsalis pedis artery, which branches repeatedly and provides blood to the tarsal and dorsal regions of the foot. The posterior tibial artery provides blood to the muscles and integument on the posterior surface of the tibial region. The fibular or peroneal artery branches from the posterior tibial artery. It bifurcates and becomes the medial plantar artery and lateral plantar artery, providing blood to the plantar surfaces. There is an anastomosis with the dorsalis pedis artery, and the medial and lateral plantar arteries form two arches called the dorsal arch (also called the arcuate arch) and the plantar arch, which provide blood to the remainder of the foot and toes. Figure 12 show the distribution of the major systemic arteries in the lower limb. Table 8 summarizes the major systemic arteries discussed in the text.

![Flow chart]

*Figure 12. The flow chart summarizes the distribution of the systemic arteries from the external iliac artery into the lower limb.*

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral artery</td>
<td>Continuation of the external iliac artery after it passes through the body cavity; divides into several smaller branches, the lateral deep femoral artery, and the genicular artery; becomes the popliteal artery as it passes posterior to the knee</td>
</tr>
</tbody>
</table>
### Table 8. Arteries Serving the Lower Limbs

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep femoral artery</td>
<td>Branch of the femoral artery; gives rise to the lateral circumflex arteries</td>
</tr>
<tr>
<td>Lateral circumflex artery</td>
<td>Branch of the deep femoral artery; supplies blood to the deep muscles of the thigh and the ventral and lateral regions of the integument</td>
</tr>
<tr>
<td>Genicular artery</td>
<td>Branch of the femoral artery; supplies blood to the region of the knee</td>
</tr>
<tr>
<td>Popliteal artery</td>
<td>Continuation of the femoral artery posterior to the knee; branches into the anterior and posterior tibial arteries</td>
</tr>
<tr>
<td>Anterior tibial artery</td>
<td>Branches from the popliteal artery; supplies blood to the anterior tibial region; becomes the dorsalis pedis artery</td>
</tr>
<tr>
<td>Dorsalis pedis artery</td>
<td>Forms from the anterior tibial artery; branches repeatedly to supply blood to the tarsal and dorsal regions of the foot</td>
</tr>
<tr>
<td>Posterior tibial artery</td>
<td>Branches from the popliteal artery and gives rise to the fibular or peroneal artery; supplies blood to the posterior tibial region</td>
</tr>
<tr>
<td>Medial plantar artery</td>
<td>Arises from the bifurcation of the posterior tibial arteries; supplies blood to the medial plantar surfaces of the foot</td>
</tr>
<tr>
<td>Lateral plantar artery</td>
<td>Arises from the bifurcation of the posterior tibial arteries; supplies blood to the lateral plantar surfaces of the foot</td>
</tr>
<tr>
<td>Dorsal or arcuate arch</td>
<td>Formed from the anastomosis of the dorsalis pedis artery and the medial and plantar arteries; branches supply the distal portions of the foot and digits</td>
</tr>
<tr>
<td>Plantar arch</td>
<td>Formed from the anastomosis of the dorsalis pedis artery and the medial and plantar arteries; branches supply the distal portions of the foot and digits</td>
</tr>
</tbody>
</table>

### Overview of Systemic Veins

Systemic veins return blood to the right atrium. Since the blood has already passed through the systemic capillaries, it will be relatively low in oxygen concentration. In many cases, there will be veins draining organs and regions of the body with the same name as the arteries that supplied these regions and the two often parallel one another. This is often described as a “complementary” pattern. However, there is a great deal more variability in the venous circulation than normally occurs in the arteries. For the sake of brevity and clarity, this text will discuss only the most commonly encountered patterns. However, keep this variation in mind when you move from the classroom to clinical practice.

In both the neck and limb regions, there are often both superficial and deeper levels of veins. The deeper veins generally correspond to the complementary arteries. The superficial veins do not normally have direct arterial counterparts, but in addition to returning blood, they also make contributions to the maintenance of body temperature. When the ambient temperature is warm, more blood is diverted to the superficial veins where heat can be more easily dissipated to the environment. In colder weather, there is more constriction of the superficial veins and blood is diverted deeper where the body can retain more of the heat.
Anatomy

The “Voyage of Discovery” analogy and stick drawings mentioned earlier remain valid techniques for the study of systemic veins, but veins present a more difficult challenge because there are numerous anastomoses and multiple branches. It is like following a river with many tributaries and channels, several of which interconnect. Tracing blood flow through arteries follows the current in the direction of blood flow, so that we move from the heart through the large arteries and into the smaller arteries to the capillaries. From the capillaries, we move into the smallest veins and follow the direction of blood flow into larger veins and back to the heart. Figure 13 outlines the path of the major systemic veins.

Figure 13. The major systemic veins of the body are shown here in an anterior view.

The right atrium receives all of the systemic venous return. Most of the blood flows into either the superior vena cava or inferior vena cava. If you draw an imaginary line at the level of the diaphragm, systemic venous circulation from above that line will generally flow into the superior vena cava; this includes blood from the head, neck, chest, shoulders, and upper limbs. The exception to this is that most venous blood flow from the coronary veins flows
directly into the coronary sinus and from there directly into the right atrium. Beneath the diaphragm, systemic venous flow enters the inferior vena cava, that is, blood from the abdominal and pelvic regions and the lower limbs.

The Superior Vena Cava

The superior vena cava drains most of the body superior to the diaphragm. On both the left and right sides, the subclavian vein forms when the axillary vein passes through the body wall from the axillary region. It fuses with the external and internal jugular veins from the head and neck to form the brachiocephalic vein. Each vertebral vein also flows into the brachiocephalic vein close to this fusion. These veins arise from the base of the brain and the cervical region of the spinal cord, and flow largely through the intervertebral foramina in the cervical vertebrae. They are the counterparts of the vertebral arteries. Each internal thoracic vein, also known as an internal mammary vein, drains the anterior surface of the chest wall and flows into the brachiocephalic vein.

The remainder of the blood supply from the thorax drains into the azygos vein. Each intercostal vein drains muscles of the thoracic wall, each esophageal vein delivers blood from the inferior portions of the esophagus, each bronchial vein drains the systemic circulation from the lungs, and several smaller veins drain the mediastinal region. Bronchial veins carry approximately 13 percent of the blood that flows into the bronchial arteries; the remainder intermingles with the pulmonary circulation and returns to the heart via the pulmonary veins. These veins flow into the azygos vein, and with the smaller hemiazygos vein (hemi- = “half”) on the left of the vertebral column, drain blood from the thoracic region. The hemiazygos vein does not drain directly into the superior vena cava but enters the brachiocephalic vein via the superior intercostal vein.

The azygos vein passes through the diaphragm from the thoracic cavity on the right side of the vertebral column and begins in the lumbar region of the thoracic cavity. It flows into the superior vena cava at approximately the level of T2, making a significant contribution to the flow of blood. It combines with the two large left and right brachiocephalic veins to form the superior vena cava.

Figure 14 and Table 9 summarize the veins of the thoracic region that flow into the superior vena cava.

Figure 14. Veins of the thoracic and abdominal regions drain blood from the area above the diaphragm, returning it to the right atrium via the
Table 9. Veins of the Thoracic Region

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior vena cava</td>
<td>Large systemic vein; drains blood from most areas superior to the diaphragm; empties into the right atrium</td>
</tr>
<tr>
<td>Subclavian vein</td>
<td>Located deep in the thoracic cavity; formed by the axillary vein as it enters the thoracic cavity from the axillary region; drains the axillary and smaller local veins near the scapular region and leads to the brachiocephalic vein</td>
</tr>
<tr>
<td>Brachiocephalic veins</td>
<td>Pair of veins that form from a fusion of the external and internal jugular veins and the subclavian vein; subclavian, external and internal jugulars, vertebral, and internal thoracic veins flow into it; drain the upper thoracic region and lead to the superior vena cava</td>
</tr>
<tr>
<td>Vertebral vein</td>
<td>Arises from the base of the brain and the cervical region of the spinal cord; passes through the intervertebral foramina in the cervical vertebrae; drains smaller veins from the cranium, spinal cord, and vertebrae, and leads to the brachiocephalic vein; counterpart of the vertebral artery</td>
</tr>
<tr>
<td>Internal thoracic veins</td>
<td>Also called internal mammary veins; drain the anterior surface of the chest wall and lead to the brachiocephalic vein</td>
</tr>
<tr>
<td>Intercostal vein</td>
<td>Drains the muscles of the thoracic wall and leads to the azygos vein</td>
</tr>
<tr>
<td>Esophageal vein</td>
<td>Drains the inferior portions of the esophagus and leads to the azygos vein</td>
</tr>
<tr>
<td>Bronchial vein</td>
<td>Drains the systemic circulation from the lungs and leads to the azygos vein</td>
</tr>
<tr>
<td>Azygos vein</td>
<td>Originates in the lumbar region and passes through the diaphragm into the thoracic cavity on the right side of the vertebral column; drains blood from the intercostal veins, esophageal veins, bronchial veins, and other veins draining the mediastinal region, and leads to the superior vena cava</td>
</tr>
<tr>
<td>Hemiazygos vein</td>
<td>Smaller vein complementary to the azygos vein; drains the esophageal veins from the esophagus and the left intercostal veins, and leads to the brachiocephalic vein via the superior intercostal vein</td>
</tr>
</tbody>
</table>

Veins of the Head and Neck

Blood from the brain and the superficial facial vein flow into each internal jugular vein. Blood from the more superficial portions of the head, scalp, and cranial regions, including the temporal vein and maxillary vein, flow into each external jugular vein. Although the external and internal jugular veins are separate vessels, there are anastomoses between them close to the thoracic region. Blood from the external jugular vein empties into the subclavian vein. Table 10 summarizes the major veins of the head and neck.
Table 10. Major Veins of the Head and Neck

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal jugular vein</td>
<td>Parallel to the common carotid artery, which is more or less its counterpart, and passes through the jugular foramen and canal; primarily drains blood from the brain, receives the superficial facial vein, and empties into the subclavian vein</td>
</tr>
<tr>
<td>Temporal vein</td>
<td>Drains blood from the temporal region and flows into the external jugular vein</td>
</tr>
<tr>
<td>Maxillary vein</td>
<td>Drains blood from the maxillary region and flows into the external jugular vein</td>
</tr>
<tr>
<td>External jugular vein</td>
<td>Drains blood from the more superficial portions of the head, scalp, and cranial regions, and leads to the subclavian vein</td>
</tr>
</tbody>
</table>

Venous Drainage of the Brain

Circulation to the brain is both critical and complex. Many smaller veins of the brain stem and the superficial veins of the cerebrum lead to larger vessels referred to as intracranial sinuses. These include the superior and inferior sagittal sinuses, straight sinus, cavernous sinuses, left and right sinuses, the petrosal sinuses, and the occipital sinuses. Ultimately, sinuses will lead back to either the inferior jugular vein or vertebral vein.

Most of the veins on the superior surface of the cerebrum flow into the largest of the sinuses, the **superior sagittal sinus**. It is located midsagittally between the meningeal and periosteal layers of the dura mater within the falx cerebri and, at first glance in images or models, can be mistaken for the subarachnoid space. Most reabsorption of cerebrospinal fluid occurs via the chorionic villi (arachnoid granulations) into the superior sagittal sinus. Blood from most of the smaller vessels originating from the inferior cerebral veins flows into the **great cerebral vein** and into the **straight sinus**. Other cerebral veins and those from the eye socket flow into the **cavernous sinus**, which flows into the **petrosal sinus** and then into the internal jugular vein. The **occipital sinus**, sagittal sinus, and straight sinuses all flow into the left and right transverse sinuses near the lambdoid suture. The **transverse sinuses** in turn flow into the **sigmoid sinuses** that pass through the jugular foramen and into the internal jugular vein. The internal jugular vein flows parallel to the common carotid artery and is more or less its counterpart. It empties into the brachiocephalic vein. The veins draining the cervical vertebrae and the posterior surface of the skull, including some blood from the occipital sinus, flow into the vertebral veins. These parallel the vertebral arteries and travel through the transverse foramina of the cervical vertebrae. The vertebral veins also flow into the brachiocephalic veins. Figure 15 and Table 11 summarize the major veins of the brain.
Figure 15. This left lateral view shows the veins of the head and neck, including the intercranial sinuses.

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior sagittal sinus</td>
<td>Enlarged vein located midsagittally between the meningeal and periosteal layers of the dura mater within the falx cerebri; receives most of the blood drained from the superior surface of the cerebrum and leads to the inferior jugular vein and the vertebral vein</td>
</tr>
<tr>
<td>Great cerebral vein</td>
<td>Receives most of the smaller vessels from the inferior cerebral veins and leads to the straight sinus</td>
</tr>
<tr>
<td>Straight sinus</td>
<td>Enlarged vein that drains blood from the brain; receives most of the blood from the great cerebral vein and leads to the left or right transverse sinus</td>
</tr>
<tr>
<td>Cavernous sinus</td>
<td>Enlarged vein that receives blood from most of the other cerebral veins and the eye socket, and leads to the petrosal sinus</td>
</tr>
<tr>
<td>Petrosal sinus</td>
<td>Enlarged vein that receives blood from the cavernous sinus and leads into the internal jugular veins</td>
</tr>
<tr>
<td>Occipital sinus</td>
<td>Enlarged vein that drains the occipital region near the falx cerebelli and leads to the left and right transverse sinuses, and also the vertebral veins</td>
</tr>
</tbody>
</table>
Table 11. Major Veins of the Brain

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transverse sinuses</td>
<td>Pair of enlarged veins near the lambdoid suture that drains the occipital, sagittal, and straight sinuses, and leads to the sigmoid sinuses</td>
</tr>
<tr>
<td>Sigmoid sinuses</td>
<td>Enlarged vein that receives blood from the transverse sinuses and leads through the jugular foramen to the internal jugular vein</td>
</tr>
</tbody>
</table>

Veins Draining the Upper Limbs

The digital veins in the fingers come together in the hand to form the palmar venous arches (Figure 16). From here, the veins come together to form the radial vein, the ulnar vein, and the median antebrachial vein. The radial vein and the ulnar vein parallel the bones of the forearm and join together at the antebrachium to form the brachial vein, a deep vein that flows into the axillary vein in the brachium.

The median antebrachial vein parallels the ulnar vein, is more medial in location, and joins the basilic vein in the forearm. As the basilic vein reaches the antecubital region, it gives off a branch called the median cubital vein that crosses at an angle to join the cephalic vein. The median cubital vein is the most common site for drawing venous blood in humans. The basilic vein continues through the arm medially and superficially to the axillary vein.

The cephalic vein begins in the antebrachium and drains blood from the superficial surface of the arm into the axillary vein. It is extremely superficial and easily seen along the surface of the biceps brachii muscle in individuals with good muscle tone and in those without excessive subcutaneous adipose tissue in the arms.

The subscapular vein drains blood from the subscapular region and joins the cephalic vein to form the axillary vein. As it passes through the body wall and enters the thorax, the axillary vein becomes the subclavian vein.

Many of the larger veins of the thoracic and abdominal region and upper limb are further represented in the flow chart below. Figure 17 and Table 12 summarize the veins of the upper limbs.

![Diagram of veins draining the upper limb](image)
Figure 17. The flow chart summarizes the distribution of the veins flowing into the superior vena cava.

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digital veins</td>
<td>Drain the digits and lead to the palmar arches of the hand and dorsal venous arch of the foot</td>
</tr>
<tr>
<td>Palmar venous arches</td>
<td>Drain the hand and digits, and lead to the radial vein, ulnar veins, and the median antebrachial vein</td>
</tr>
<tr>
<td>Radial vein</td>
<td>Vein that parallels the radius and radial artery; arises from the palmar venous arches and leads to the brachial vein</td>
</tr>
<tr>
<td>Ulnar vein</td>
<td>Vein that parallels the ulna and ulnar artery; arises from the palmar venous arches and leads to the brachial vein</td>
</tr>
<tr>
<td>Brachial vein</td>
<td>Deeper vein of the arm that forms from the radial and ulnar veins in the lower arm; leads to the axillary vein</td>
</tr>
</tbody>
</table>
Table 12. Veins of the Upper Limbs

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median antebrachial vein</td>
<td>Vein that parallels the ulnar vein but is more medial in location; intertwines with the palmar venous arches; leads to the basilic vein</td>
</tr>
<tr>
<td>Basilic vein</td>
<td>Superficial vein of the arm that arises from the median antebrachial vein, intersects with the median cubital vein, parallels the ulnar vein, and continues into the upper arm; along with the brachial vein, it leads to the axillary vein</td>
</tr>
<tr>
<td>Median cubital vein</td>
<td>Superficial vessel located in the antecubital region that links the cephalic vein to the basilic vein in the form of a v; a frequent site from which to draw blood</td>
</tr>
<tr>
<td>Cephalic vein</td>
<td>Superficial vessel in the upper arm; leads to the axillary vein</td>
</tr>
<tr>
<td>Subscapular vein</td>
<td>Drains blood from the subscapular region and leads to the axillary vein</td>
</tr>
<tr>
<td>Axillary vein</td>
<td>The major vein in the axillary region; drains the upper limb and becomes the subclavian vein</td>
</tr>
</tbody>
</table>

The Inferior Vena Cava

Other than the small amount of blood drained by the azygos and hemiazygos veins, most of the blood inferior to the diaphragm drains into the inferior vena cava before it is returned to the heart (see Figure 15). Lying just beneath the parietal peritoneum in the abdominal cavity, the inferior vena cava parallels the abdominal aorta, where it can receive blood from abdominal veins. The lumbar portions of the abdominal wall and spinal cord are drained by a series of lumbar veins, usually four on each side. The ascending lumbar veins drain into either the azygos vein on the right or the hemiazygos vein on the left, and return to the superior vena cava. The remaining lumbar veins drain directly into the inferior vena cava.

Blood supply from the kidneys flows into each renal vein, normally the largest veins entering the inferior vena cava. A number of other, smaller veins empty into the left renal vein. Each adrenal vein drains the adrenal or suprarenal glands located immediately superior to the kidneys. The right adrenal vein enters the inferior vena cava directly, whereas the left adrenal vein enters the left renal vein.

From the male reproductive organs, each testicular vein flows from the scrotum, forming a portion of the spermatic cord. Each ovarian vein drains an ovary in females. Each of these veins is generically called a gonadal vein. The right gonadal vein empties directly into the inferior vena cava, and the left gonadal vein empties into the left renal vein.

Each side of the diaphragm drains into a phrenic vein; the right phrenic vein empties directly into the inferior vena cava, whereas the left phrenic vein empties into the left renal vein. Blood supply from the liver drains into each hepatic vein and directly into the inferior vena cava. Since the inferior vena cava lies primarily to the right of the vertebral column and aorta, the left renal vein is longer, as are the left phrenic, adrenal, and gonadal veins. The longer length of the left renal vein makes the left kidney the primary target of surgeons removing this organ for donation. Figure 18 provides a flow chart of the veins flowing into the inferior vena cava. Table 13 summarizes the major veins of the abdominal region.
Figure 18. The flow chart summarizes veins that deliver blood to the inferior vena cava.

Table 13. Major Veins of the Abdominal Region

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior vena cava</td>
<td>Large systemic vein that drains blood from areas largely inferior to the diaphragm; empties into the right atrium</td>
</tr>
<tr>
<td>Lumbar veins</td>
<td>Series of veins that drain the lumbar portion of the abdominal wall and spinal cord; the ascending lumbar veins drain into the azygos vein on the right or the hemiazygos vein on the left; the remaining lumbar veins drain directly into the inferior vena cava</td>
</tr>
<tr>
<td>Renal vein</td>
<td>Largest vein entering the inferior vena cava; drains the kidneys and flows into the inferior vena cava</td>
</tr>
</tbody>
</table>
Table 13. Major Veins of the Abdominal Region

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal vein</td>
<td>Drains the adrenal or suprarenal; the right adrenal vein enters the inferior vena cava directly and the left adrenal vein enters the left renal vein</td>
</tr>
<tr>
<td>Testicular vein</td>
<td>Drains the testes and forms part of the spermatic cord; the right testicular vein empties directly into the inferior vena cava and the left testicular vein empties into the left renal vein</td>
</tr>
<tr>
<td>Ovarian vein</td>
<td>Drains the ovary; the right ovarian vein empties directly into the inferior vena cava and the left ovarian vein empties into the left renal vein</td>
</tr>
<tr>
<td>Gonadal vein</td>
<td>Generic term for a vein draining a reproductive organ; may be either an ovarian vein or a testicular vein, depending on the sex of the individual</td>
</tr>
<tr>
<td>Phrenic vein</td>
<td>Drains the diaphragm; the right phrenic vein flows into the inferior vena cava and the left phrenic vein empties into the left renal vein</td>
</tr>
<tr>
<td>Hepatic vein</td>
<td>Drains systemic blood from the liver and flows into the inferior vena cava</td>
</tr>
</tbody>
</table>

Veins Draining the Lower Limbs

The superior surface of the foot drains into the digital veins, and the inferior surface drains into the plantar veins, which flow into a complex series of anastomoses in the feet and ankles, including the dorsal venous arch and the plantar venous arch. From the dorsal venous arch, blood supply drains into the anterior and posterior tibial veins. The anterior tibial vein drains the area near the tibialis anterior muscle and combines with the posterior tibial vein and the fibular vein to form the popliteal vein. The posterior tibial vein drains the posterior surface of the tibia and joins the popliteal vein. The fibular vein drains the muscles and integument in proximity to the fibula and also joins the popliteal vein. The small saphenous vein located on the lateral surface of the leg drains blood from the superficial regions of the lower leg and foot, and flows into to the popliteal vein. As the popliteal vein passes behind the knee in the popliteal region, it becomes the femoral vein. It is palpable in patients without excessive adipose tissue.
Figure 19. Anterior and posterior views show the major veins that drain the lower limb into the inferior vena cava.

Close to the body wall, the great saphenous vein, the deep femoral vein, and the femoral circumflex vein drain into the femoral vein. The great saphenous vein is a prominent surface vessel located on the medial surface of the leg and thigh that collects blood from the superficial portions of these areas. The deep femoral vein, as the name suggests, drains blood from the deeper portions of the thigh. The femoral circumflex vein forms a loop around the femur just inferior to the trochanters and drains blood from the areas in proximity to the head and neck of the femur.

As the femoral vein penetrates the body wall from the femoral portion of the upper limb, it becomes the external iliac vein, a large vein that drains blood from the leg to the common iliac vein. The pelvic organs and integument drain into the internal iliac vein, which forms from several smaller veins in the region, including the umbilical veins that run on either side of the bladder. The external and internal iliac veins combine near the inferior portion of the sacroiliac joint to form the common iliac vein. In addition to blood supply from the external and internal iliac veins, the middle sacral vein drains the sacral region into the common iliac vein. Similar to the common iliac arteries, the common iliac veins come together at the level of L5 to form the inferior vena cava.

Figure 20 is a flow chart of veins flowing into the lower limb. Table 14 summarizes the major veins of the lower limbs.
Figure 20. The flow chart summarizes venous flow from the lower limb.

Table 14. Veins of the Lower Limbs

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plantar veins</td>
<td>Drain the foot and flow into the plantar venous arch</td>
</tr>
<tr>
<td>Dorsal venous arch</td>
<td>Drains blood from digital veins and vessels on the superior surface of the foot</td>
</tr>
<tr>
<td>Plantar venous arch</td>
<td>Formed from the plantar veins; flows into the anterior and posterior tibial veins through anastomoses</td>
</tr>
<tr>
<td>Anterior tibial vein</td>
<td>Formed from the dorsal venous arch; drains the area near the tibialis anterior muscle and flows into the popliteal vein</td>
</tr>
<tr>
<td>Posterior tibial vein</td>
<td>Formed from the dorsal venous arch; drains the area near the posterior surface of the tibia and flows into the popliteal vein</td>
</tr>
<tr>
<td>Fibular vein</td>
<td>Drains the muscles and integument near the fibula and flows into the popliteal vein</td>
</tr>
</tbody>
</table>
### Table 14. Veins of the Lower Limbs

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small saphenous vein</td>
<td>Located on the lateral surface of the leg; drains blood from the superficial regions of the lower leg and foot, and flows into the popliteal vein</td>
</tr>
<tr>
<td>Popliteal vein</td>
<td>Drains the region behind the knee and forms from the fusion of the fibular, anterior, and posterior tibial veins; flows into the femoral vein</td>
</tr>
<tr>
<td>Great saphenous vein</td>
<td>Prominent surface vessel located on the medial surface of the leg and thigh; drains the superficial portions of these areas and flows into the femoral vein</td>
</tr>
<tr>
<td>Deep femoral vein</td>
<td>Drains blood from the deeper portions of the thigh and flows into the femoral vein</td>
</tr>
<tr>
<td>Femoral circumflex vein</td>
<td>Forms a loop around the femur just inferior to the trochanters; drains blood from the areas around the head and neck of the femur; flows into the femoral vein</td>
</tr>
<tr>
<td>Femoral vein</td>
<td>Drains the upper leg; receives blood from the great saphenous vein, the deep femoral vein, and the femoral circumflex vein; becomes the external iliac vein when it crosses the body wall</td>
</tr>
<tr>
<td>External iliac vein</td>
<td>Formed when the femoral vein passes into the body cavity; drains the legs and flows into the common iliac vein</td>
</tr>
<tr>
<td>Internal iliac vein</td>
<td>Drains the pelvic organs and integument; formed from several smaller veins in the region; flows into the common iliac vein</td>
</tr>
<tr>
<td>Middle sacral vein</td>
<td>Drains the sacral region and flows into the left common iliac vein</td>
</tr>
<tr>
<td>Common iliac vein</td>
<td>Flows into the inferior vena cava at the level of L5; the left common iliac vein drains the sacral region; formed from the union of the external and internal iliac veins near the inferior portion of the sacroiliac joint</td>
</tr>
</tbody>
</table>

### Hepatic Portal System
The liver is a complex biochemical processing plant. It packages nutrients absorbed by the digestive system; produces plasma proteins, clotting factors, and bile; and disposes of worn-out cell components and waste products. Instead of entering the circulation directly, absorbed nutrients and certain wastes (for example, materials produced by the spleen) travel to the liver for processing. They do so via the hepatic portal system. Portal systems begin and end in capillaries. In this case, the initial capillaries from the stomach, small intestine, large intestine, and spleen lead to the hepatic portal vein and end in specialized capillaries within the liver, the hepatic sinusoids. You saw the only other portal system with the hypothalamic-hypophyseal portal vessel in the endocrine chapter.

The hepatic portal system consists of the hepatic portal vein and the veins that drain into it. The hepatic portal vein itself is relatively short, beginning at the level of L2 with the confluence of the superior mesenteric and splenic veins. It also receives branches from the inferior mesenteric vein, plus the splenic veins and all their tributaries. The superior mesenteric vein receives blood from the small intestine, two-thirds of the large intestine, and the stomach. The inferior mesenteric vein drains the distal third of the large intestine, including the descending colon, the sigmoid colon, and the rectum. The splenic vein is formed from branches from the spleen, pancreas, and portions of the stomach, and the inferior mesenteric vein. After its formation, the hepatic portal vein also receives branches from the gastric veins of the stomach and cystic veins from the gall bladder. The hepatic portal vein delivers materials from these digestive and circulatory organs directly to the liver for processing.

Because of the hepatic portal system, the liver receives its blood supply from two different sources: from normal systemic circulation via the hepatic artery and from the hepatic portal vein. The liver processes the blood from the portal system to remove certain wastes and excess nutrients, which are stored for later use. This processed blood, as well as the systemic blood that came from the hepatic artery, exits the liver via the right, left, and middle hepatic veins, and flows into the inferior vena cava. Overall systemic blood composition remains relatively stable, since the liver is able to metabolize the absorbed digestive components.

Figure 22. The liver receives blood from the normal systemic circulation via the hepatic artery. It also receives and processes blood from other organs, delivered via the veins of the hepatic portal system. All blood exits the liver via the hepatic vein, which delivers the blood to the inferior vena cava. (Different colors are used to help distinguish among the different vessels in the system.)
Chapter Review

The right ventricle pumps oxygen-depleted blood into the pulmonary trunk and right and left pulmonary arteries, which carry it to the right and left lungs for gas exchange. Oxygen-rich blood is transported by pulmonary veins to the left atrium. The left ventricle pumps this blood into the aorta. The main regions of the aorta are the ascending aorta, aortic arch, and descending aorta, which is further divided into the thoracic and abdominal aorta. The coronary arteries branch from the ascending aorta. After oxygenating tissues in the capillaries, systemic blood is returned to the right atrium from the venous system via the superior vena cava, which drains most of the veins superior to the diaphragm, the inferior vena cava, which drains most of the veins inferior to the diaphragm, and the coronary veins via the coronary sinus. The hepatic portal system carries blood to the liver for processing before it enters circulation. Review the figures provided in this section for circulation of blood through the blood vessels.

Critical Thinking Questions

Identify the ventricle of the heart that pumps oxygen-depleted blood and the arteries of the body that carry oxygen-depleted blood.
What organs do the gonadal veins drain?
What arteries play the leading roles in supplying blood to the brain?

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Development of Blood Vessels and Fetal Circulation

Learning Objectives

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

- Describe the development of blood vessels
- Describe the fetal circulation

In a developing embryo, the heart has developed enough by day 21 post-fertilization to begin beating. Circulation patterns are clearly established by the fourth week of embryonic life. It is critical to the survival of the developing human that the circulatory system forms early to supply the growing tissue with nutrients and gases, and to remove waste products. Blood cells and vessel production in structures outside the embryo proper called the yolk sac, chorion, and connecting stalk begin about 15 to 16 days following fertilization. Development of these circulatory elements within the embryo itself begins approximately 2 days later. You will learn more about the formation and function of these early structures when you study the chapter on development. During those first few weeks, blood vessels begin to form from the embryonic mesoderm. The precursor cells are known as hemangioblasts. These in turn differentiate into angioblasts, which give rise to the blood vessels and pluripotent stem cells, which differentiate into the formed elements of blood. (Seek additional content for more detail on fetal development and circulation.) Together, these cells form masses known as blood islands scattered throughout the embryonic disc. Spaces appear on the blood islands that develop into vessel lumens. The endothelial lining of the vessels arise from the angioblasts within these islands. Surrounding mesenchymal cells give rise to the smooth muscle and connective tissue layers of the vessels. While the vessels are developing, the pluripotent stem cells begin to form the blood.

Vascular tubes also develop on the blood islands, and they eventually connect to one another as well as to the developing, tubular heart. Thus, the developmental pattern, rather than beginning from the formation of one central vessel and spreading outward, occurs in many regions simultaneously with vessels later joining together. This angiogenesis—the creation of new blood vessels from existing ones—continues as needed throughout life as we grow and develop.

Blood vessel development often follows the same pattern as nerve development and travels to the same target tissues and organs. This occurs because the many factors directing growth of nerves also stimulate blood vessels to follow a similar pattern. Whether a given vessel develops into an artery or a vein is dependent upon local concentrations of signaling proteins.

As the embryo grows within the mother’s uterus, its requirements for nutrients and gas exchange also grow. The placenta—a circulatory organ unique to pregnancy—develops jointly from the embryo and uterine wall structures to fill this need. Emerging from the placenta is the umbilical vein, which carries oxygen-rich blood from the mother to the fetal inferior vena cava via the ductus venosus to the heart that pumps it into fetal circulation. Two umbilical arteries carry oxygen-depleted fetal blood, including wastes and carbon dioxide, to the placenta. Remnants of the umbilical arteries remain in the adult. (Seek additional content for more information on the role of the placenta in fetal circulation.)

There are three major shunts—alternate paths for blood flow—found in the circulatory system of the fetus. Two of these shunts divert blood from the pulmonary to the systemic circuit, whereas the third connects the umbilical vein to the inferior vena cava. The first two shunts are critical during fetal life, when the lungs are compressed, filled with amniotic fluid, and nonfunctional, and gas exchange is provided by the placenta. These shunts close shortly after birth, however, when the newborn begins to breathe. The third shunt persists a bit longer but
becomes nonfunctional once the umbilical cord is severed. The three shunts are as follows:

- **The foramen ovale** is an opening in the interatrial septum that allows blood to flow from the right atrium to the left atrium. A valve associated with this opening prevents backflow of blood during the fetal period. As the newborn begins to breathe and blood pressure in the atria increases, this shunt closes. The fossa ovalis remains in the interatrial septum after birth, marking the location of the former foramen ovale.

- **The ductus arteriosus** is a short, muscular vessel that connects the pulmonary trunk to the aorta. Most of the blood pumped from the right ventricle into the pulmonary trunk is thereby diverted into the aorta. Only enough blood reaches the fetal lungs to maintain the developing lung tissue. When the newborn takes the first breath, pressure within the lungs drops dramatically, and both the lungs and the pulmonary vessels expand. As the amount of oxygen increases, the smooth muscles in the wall of the ductus arteriosus constrict, sealing off the passage. Eventually, the muscular and endothelial components of the ductus arteriosus degenerate, leaving only the connective tissue component of the ligamentum arteriosum.

- **The ductus venosus** is a temporary blood vessel that branches from the umbilical vein, allowing much of the freshly oxygenated blood from the placenta—the organ of gas exchange between the mother and fetus—to bypass the fetal liver and go directly to the fetal heart. The ductus venosus closes slowly during the first weeks of infancy and degenerates to become the ligamentum venosum.

![Figure 1. The foramen ovale in the interatrial septum allows blood to flow from the right atrium to the left atrium. The ductus arteriosus is a temporary vessel, connecting the aorta to the pulmonary trunk. The ductus venosus links the umbilical vein to the inferior vena cava largely through the liver.](image-url)
Chapter Review

Blood vessels begin to form from the embryonic mesoderm. The precursor hemangioblasts differentiate into angioblasts, which give rise to the blood vessels and pluripotent stem cells that differentiate into the formed elements of the blood. Together, these cells form blood islands scattered throughout the embryo. Extensions known as vascular tubes eventually connect the vascular network. As the embryo grows within the mother’s womb, the placenta develops to supply blood rich in oxygen and nutrients via the umbilical vein and to remove wastes in oxygen-depleted blood via the umbilical arteries. Three major shunts found in the fetus are the foramen ovale and ductus arteriosus, which divert blood from the pulmonary to the systemic circuit, and the ductus venosus, which carries freshly oxygenated blood high in nutrients to the fetal heart.

Critical Thinking Questions

All tissues, including malignant tumors, need a blood supply. Explain why drugs called angiogenesis inhibitors would be used in cancer treatment.

Explain the location and importance of the ductus arteriosus in fetal circulation.

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Section 19: The Lymphatic and Immune System
Introduction to the Lymphatic and Immune System

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

- Identify the components and anatomy of the lymphatic system
- Discuss the role of the innate immune response against pathogens
- Describe the power of the adaptive immune response to cure disease
- Explain immunological deficiencies and over-reactions of the immune system
- Discuss the role of the immune response in transplantation and cancer
- Describe the interaction of the immune and lymphatic systems with other body systems

In June 1981, the Centers for Disease Control and Prevention (CDC), in Atlanta, Georgia, published a report of an unusual cluster of five patients in Los Angeles, California. All five were diagnosed with a rare pneumonia caused by a fungus called *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*).

Why was this unusual? Although commonly found in the lungs of healthy individuals, this fungus is an opportunistic pathogen that causes disease in individuals with suppressed or underdeveloped immune systems. The very young, whose immune systems have yet to mature, and the elderly, whose immune systems have declined with age, are particularly susceptible. The five patients from LA, though, were between 29 and 36 years of age and should have been in the prime of their lives, immunologically speaking. What could be going on?

A few days later, a cluster of

Figure 1. (a) As of 2008, more than 15 percent of adults were infected with HIV in certain African countries. This grim picture had changed little by 2012. (b) In this scanning electron micrograph, HIV virions (green particles) are budding off the surface of a macrophage (pink structure). (credit b: C. Goldsmith)
eight cases was reported in New York City, also involving young patients, this time exhibiting a rare form of skin cancer known as Kaposi’s sarcoma. This cancer of the cells that line the blood and lymphatic vessels was previously observed as a relatively innocuous disease of the elderly. The disease that doctors saw in 1981 was frighteningly more severe, with multiple, fast-growing lesions that spread to all parts of the body, including the trunk and face. Could the immune systems of these young patients have been compromised in some way? Indeed, when they were tested, they exhibited extremely low numbers of a specific type of white blood cell in their bloodstream, indicating that they had somehow lost a major part of the immune system.

Acquired immune deficiency syndrome, or AIDS, turned out to be a new disease caused by the previously unknown human immunodeficiency virus (HIV). Although nearly 100 percent fatal in those with active HIV infections in the early years, the development of anti-HIV drugs has transformed HIV infection into a chronic, manageable disease and not the certain death sentence it once was. One positive outcome resulting from the emergence of HIV disease was that the public’s attention became focused as never before on the importance of having a functional and healthy immune system.

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Anatomy

Anatomy of the Lymphatic and Immune Systems

Learning Objectives

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

- Describe the structure and function of the lymphatic tissue (lymph fluid, vessels, ducts, and organs)
- Describe the structure and function of the primary and secondary lymphatic organs
- Discuss the cells of the immune system, how they function, and their relationship with the lymphatic system

The **immune system** is the complex collection of cells and organs that destroys or neutralizes pathogens that would otherwise cause disease or death. The lymphatic system, for most people, is associated with the immune system to such a degree that the two systems are virtually indistinguishable. The **lymphatic system** is the system of vessels, cells, and organs that carries excess fluids to the bloodstream and filters pathogens from the blood. The swelling of lymph nodes during an infection and the transport of lymphocytes via the lymphatic vessels are but two examples of the many connections between these critical organ systems.

Functions of the Lymphatic System

A major function of the lymphatic system is to drain body fluids and return them to the bloodstream. Blood pressure causes leakage of fluid from the capillaries, resulting in the accumulation of fluid in the interstitial space—that is, spaces between individual cells in the tissues. In humans, 20 liters of plasma is released into the interstitial space of the tissues each day due to capillary filtration. Once this filtrate is out of the bloodstream and in the tissue spaces, it is referred to as interstitial fluid. Of this, 17 liters is reabsorbed directly by the blood vessels. But what happens to the remaining three liters? This is where the lymphatic system comes into play. It drains the excess fluid and empties it back into the bloodstream via a series of vessels, trunks, and ducts. **Lymph** is the term used to describe interstitial fluid once it has entered the lymphatic system. When the lymphatic system is damaged in some way, such as by being blocked by cancer cells or destroyed by injury, protein-rich interstitial fluid accumulates (sometimes “backs up” from the lymph vessels) in the tissue spaces. This inappropriate accumulation of fluid referred to as lymphedema may lead to serious medical consequences.

As the vertebrate immune system evolved, the network of lymphatic vessels became convenient avenues for transporting the cells of the immune system. Additionally, the transport of dietary lipids and fat-soluble vitamins absorbed in the gut uses this system.

Cells of the immune system not only use lymphatic vessels to make their way from interstitial spaces back into the circulation, but they also use lymph nodes as major staging areas for the development of critical immune responses. A **lymph node** is one of the small, bean-shaped organs located throughout the lymphatic system.

Practice Questions

What are the three main components of the lymphatic system?
Structure of the Lymphatic System

The lymphatic vessels begin as open-ended capillaries, which feed into larger and larger lymphatic vessels, and eventually empty into the bloodstream by a series of ducts. Along the way, the lymph travels through the lymph nodes, which are commonly found near the groin, armpits, neck, chest, and abdomen. Humans have about 500–600 lymph nodes throughout the body.

A major distinction between the lymphatic and cardiovascular systems in humans is that lymph is not actively pumped by the heart, but is forced through the vessels by the movements of the body, the contraction of skeletal muscles during body movements, and breathing. One-way valves (semi-lunar valves) in lymphatic vessels keep the lymph moving toward the heart. Lymph flows from the lymphatic capillaries, through lymphatic vessels, and then is dumped into the circulatory system via the lymphatic ducts located at the junction of the jugular and subclavian veins in the neck.
Lymphatic Capillaries

**Lymphatic capillaries**, also called the terminal lymphatics, are vessels where interstitial fluid enters the lymphatic system to become lymph fluid. Located in almost every tissue in the body, these vessels are interlaced among the arterioles and venules of the circulatory system in the soft connective tissues of the body. Exceptions are the central nervous system, bone marrow, bones, teeth, and the cornea of the eye, which do not contain lymph vessels.

![Lymphatic capillaries in the tissue spaces](image)

*Figure 2. Lymphatic capillaries are interlaced with the arterioles and venules of the cardiovascular system. Collagen fibers anchor a lymphatic capillary in the tissue (inset). Interstitial fluid slips through spaces between the overlapping endothelial cells that compose the lymphatic capillary.*

Lymphatic capillaries are formed by a one cell-thick layer of endothelial cells and represent the open end of the system, allowing interstitial fluid to flow into them via overlapping cells. When interstitial pressure is low, the endothelial flaps close to prevent "backflow." As interstitial pressure increases, the spaces between the cells open up, allowing the fluid to enter. Entry of fluid into lymphatic capillaries is also enabled by the collagen filaments that anchor the capillaries to surrounding structures. As interstitial pressure increases, the filaments pull on the endothelial cell flaps, opening up them even further to allow easy entry of fluid.

In the small intestine, lymphatic capillaries called lacteals are critical for the transport of dietary lipids and lipid-soluble vitamins to the bloodstream. In the small intestine, dietary triglycerides combine with other lipids and proteins, and enter the lacteals to form a milky fluid called **chyle**. The chyle then travels through the lymphatic system, eventually entering the liver and then the bloodstream.

**Larger Lymphatic Vessels, Trunks, and Ducts**

The lymphatic capillaries empty into larger lymphatic vessels, which are similar to veins in terms of their three-tunic structure and the presence of valves. These one-way valves are located fairly close to one another, and each one causes a bulge in the lymphatic vessel, giving the vessels a beaded appearance.

The superficial and deep lymphatics eventually merge to form larger lymphatic vessels known as **lymphatic trunks**. On the right side of the body, the right sides of the head, thorax, and right upper limb drain lymph fluid into the right subclavian vein via the right lymphatic duct. On the left side of the body, the remaining portions of the body drain into the larger thoracic duct, which drains into the left subclavian vein. The thoracic duct itself begins just beneath the diaphragm in the **cisterna chyli**, a sac-like chamber that receives lymph from the lower
abdomen, pelvis, and lower limbs by way of the left and right lumbar trunks and the intestinal trunk.

*Figure 3. The thoracic duct drains a much larger portion of the body than does the right lymphatic duct.*

The overall drainage system of the body is asymmetrical. The right lymphatic duct receives lymph from only the upper right side of the body. The lymph from the rest of the body enters the bloodstream through the thoracic duct via all the remaining lymphatic trunks. In general, lymphatic vessels of the subcutaneous tissues of the skin, that is, the superficial lymphatics, follow the same routes as veins, whereas the deep lymphatic vessels of the viscera generally follow the paths of arteries.

The Organization of Immune Function

The immune system is a collection of barriers, cells, and soluble proteins that interact and communicate with each other in extraordinarily complex ways. The modern model of immune function is organized into three phases based on the timing of their effects. The three temporal phases consist of the following:

- **Barrier defenses** such as the skin and mucous membranes, which act instantaneously to prevent pathogenic invasion into the body tissues
- The rapid but nonspecific **innate immune response**, which consists of a variety of specialized cells and soluble factors
- The slower but more specific and effective **adaptive immune response**, which involves many cell types and soluble factors, but is primarily controlled by white blood cells (leukocytes) known as **lymphocytes**, which help control immune responses

The cells of the blood, including all those involved in the immune response, arise in the bone marrow via various differentiation pathways from hematopoietic stem cells. In contrast with embryonic stem cells, hematopoietic stem cells are present throughout adulthood and allow for the continuous differentiation of blood cells to replace those lost to age or function. These cells can be divided into three classes based on function:

- Phagocytic cells, which ingest pathogens to destroy them
- Lymphocytes, which specifically coordinate the activities of adaptive immunity
- Cells containing cytoplasmic granules, which help mediate immune responses against parasites
Lymphocytes

As stated above, lymphocytes are the primary cells of adaptive immune responses (see Table 1 for more details). The two basic types of lymphocytes, B cells and T cells, are identical morphologically with a large central nucleus surrounded by a thin layer of cytoplasm. They are distinguished from each other by their surface protein markers as well as by the molecules they secrete. While B cells mature in red bone marrow and T cells mature in the thymus, they both initially develop from bone marrow. T cells migrate from bone marrow to the thymus gland where they further mature. B cells and T cells are found in many parts of the body, circulating in the bloodstream and lymph, and residing in secondary lymphoid organs, including the spleen and lymph nodes, which will be described later in this section. The human body contains approximately $10^{12}$ lymphocytes.

B Cells

B cells are immune cells that function primarily by producing antibodies. An antibody is any of the group of proteins that binds specifically to pathogen-associated molecules known as antigens. An antigen is a chemical structure on the surface of a pathogen that binds to T or B lymphocyte antigen receptors. Once activated by binding to antigen, B cells differentiate into cells that secrete a soluble form of their surface antibodies. These activated B cells are known as plasma cells.
T Cells

The T cell, on the other hand, does not secrete antibody but performs a variety of functions in the adaptive immune response. Different T cell types have the ability to either secrete soluble factors that communicate with other cells of the adaptive immune response or destroy cells infected with intracellular pathogens. The roles of T and B lymphocytes in the adaptive immune response will be discussed further in this chapter.

Plasma Cells

Another type of lymphocyte of importance is the plasma cell. A plasma cell is a B cell that has differentiated in response to antigen binding, and has thereby gained the ability to secrete soluble antibodies. These cells differ in morphology from standard B and T cells in that they contain a large amount of cytoplasm packed with the protein-synthesizing machinery known as rough endoplasmic reticulum.

Natural Killer Cells

A fourth important lymphocyte is the natural killer cell, a participant in the innate immune response. A natural killer cell (NK) is a circulating blood cell that contains cytotoxic (cell-killing) granules in its extensive cytoplasm. It shares this mechanism with the cytotoxic T cells of the adaptive immune response. NK cells are among the body’s first lines of defense against viruses and certain types of cancer.

Table 1. Lymphocytes

<table>
<thead>
<tr>
<th>Type of lymphocyte</th>
<th>Primary function</th>
</tr>
</thead>
<tbody>
<tr>
<td>B lymphocyte</td>
<td>Generates diverse antibodies</td>
</tr>
<tr>
<td>T lymphocyte</td>
<td>Secretes chemical messengers</td>
</tr>
<tr>
<td>Plasma cell</td>
<td>Secretes antibodies</td>
</tr>
<tr>
<td>NK cell</td>
<td>Destroys virally infected cells</td>
</tr>
</tbody>
</table>

Practice Question

What is the role of the dendritic cell in an HIV infection?

Primary Lymphoid Organs and Lymphocyte Development

Understanding the differentiation and development of B and T cells is critical to the understanding of the adaptive immune response. It is through this process that the body (ideally) learns to destroy only pathogens and leaves the body’s own cells relatively intact. The primary lymphoid organs are the bone marrow, spleen, and thymus gland. The lymphoid organs are where lymphocytes mature, proliferate, and are selected, which enables them to attack pathogens without harming the cells of the body.
Bone Marrow

In the embryo, blood cells are made in the yolk sac. As development proceeds, this function is taken over by the spleen, lymph nodes, and liver. Later, the bone marrow takes over most hematopoietic functions, although the final stages of the differentiation of some cells may take place in other organs. The red bone marrow is a loose collection of cells where hematopoiesis occurs, and the yellow bone marrow is a site of energy storage, which consists largely of fat cells. The B cell undergoes nearly all of its development in the red bone marrow, whereas the immature T cell, called a thymocyte, leaves the bone marrow and matures largely in the thymus gland.

Thymus

The thymus gland is a bilobed organ found in the space between the sternum and the aorta of the heart. Connective tissue holds the lobes closely together but also separates them and forms a capsule.

Figure 5. Red bone marrow fills the head of the femur, and a spot of yellow bone marrow is visible in the center. The white reference bar is 1 cm.

Figure 6. The thymus lies above the heart. The trabeculae and lobules, including the darkly staining cortex and the lighter staining medulla of each lobule, are clearly visible in the light micrograph of the thymus of a newborn. LM × 100. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

The connective tissue capsule further divides the thymus into lobules via extensions called trabeculae. The outer region of the organ is known as the cortex and contains large numbers of thymocytes with some epithelial cells, macrophages, and dendritic cells (two types of phagocytic cells that are derived from monocytes). The cortex is
Anatomy

densely packed so it stains more intensely than the rest of the thymus. The medulla, where thymocytes migrate before leaving the thymus, contains a less dense collection of thymocytes, epithelial cells, and dendritic cells.

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Aging and the Immune System

By the year 2050, 25 percent of the population of the United States will be 60 years of age or older. The CDC estimates that 80 percent of those 60 years and older have one or more chronic disease associated with deficiencies of the immune systems. This loss of immune function with age is called immunosenescence. To treat this growing population, medical professionals must better understand the aging process. One major cause of age-related immune deficiencies is thymic involution, the shrinking of the thymus gland that begins at birth, at a rate of about three percent tissue loss per year, and continues until 35–45 years of age, when the rate declines to about one percent loss per year for the rest of one’s life. At that pace, the total loss of thymic epithelial tissue and thymocytes would occur at about 120 years of age. Thus, this age is a theoretical limit to a healthy human lifespan.

Thymic involution has been observed in all vertebrate species that have a thymus gland. Animal studies have shown that transplanted thymic grafts between inbred strains of mice involuted according to the age of the donor and not of the recipient, implying the process is genetically programmed. There is evidence that the thymic microenvironment, so vital to the development of naïve T cells, loses thymic epithelial cells according to the decreasing expression of the FOXP1 gene with age.

It is also known that thymic involution can be altered by hormone levels. Sex hormones such as estrogen and testosterone enhance involution, and the hormonal changes in pregnant women cause a temporary thymic involution that reverses itself, when the size of the thymus and its hormone levels return to normal, usually after lactation ceases. What does all this tell us? Can we reverse immunosenescence, or at least slow it down? The potential is there for using thymic transplants from younger donors to keep thymic output of naive T cells high. Gene therapies that target gene expression are also seen as future possibilities. The more we learn through immunosenescence research, the more opportunities there will be to develop therapies, even though these therapies will likely take decades to develop. The ultimate goal is for everyone to live and be healthy longer, but there may be limits to immortality imposed by our genes and hormones.

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Secondary Lymphoid Organs and their Roles in Active Immune Responses

Lymphocytes develop and mature in the primary lymphoid organs, but they mount immune responses from the secondary lymphoid organs. A naïve lymphocyte is one that has left the primary organ and entered a secondary lymphoid organ. Naïve lymphocytes are fully functional immunologically, but have yet to encounter an antigen to respond to. In addition to circulating in the blood and lymph, lymphocytes concentrate in secondary lymphoid organs, which include the lymph nodes, spleen, and lymphoid nodules. All of these tissues have many features in common, including the following:

- The presence of lymphoid follicles, the sites of the formation of lymphocytes, with specific B cell-rich and T cell-rich areas
- An internal structure of reticular fibers with associated fixed macrophages
- Germinal centers, which are the sites of rapidly dividing B lymphocytes and plasma cells, with the exception of the spleen
- Specialized post-capillary vessels known as high endothelial venules; the cells lining these venules are thicker and more columnar than normal endothelial cells, which allow cells from the blood to directly enter these tissues

Lymph Nodes

Lymph nodes function to remove debris and pathogens from the lymph, and are thus sometimes referred to as the “filters of the lymph”. Any bacteria that infect the interstitial fluid are taken up by the lymphatic capillaries and transported to a regional lymph node. Dendritic cells and macrophages within this organ internalize and kill many
of the pathogens that pass through, thereby removing them from the body. The lymph node is also the site of adaptive immune responses mediated by T cells, B cells, and accessory cells of the adaptive immune system. Like the thymus, the bean-shaped lymph nodes are surrounded by a tough capsule of connective tissue and are separated into compartments by trabeculae, the extensions of the capsule. In addition to the structure provided by the capsule and trabeculae, the structural support of the lymph node is provided by a series of reticular fibers laid down by fibroblasts.

Figure 7. Lymph nodes are masses of lymphatic tissue located along the larger lymph vessels. The micrograph of the lymph nodes shows a germinal center, which consists of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. LM × 128. (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

The major routes into the lymph node are via afferent lymphatic vessels. Cells and lymph fluid that leave the lymph node may do so by another set of vessels known as the efferent lymphatic vessels. Lymph enters the lymph node via the subcapsular sinus, which is occupied by dendritic cells, macrophages, and reticular fibers. Within the cortex of the lymph node are lymphoid follicles, which consist of germinal centers of rapidly dividing B cells surrounded by a layer of T cells and other accessory cells. As the lymph continues to flow through the node, it enters the medulla, which consists of medullary cords of B cells and plasma cells, and the medullary sinuses where the lymph collects before leaving the node via the efferent lymphatic vessels.

Spleen

In addition to the lymph nodes, the spleen is a major secondary lymphoid organ. It is about 12 cm (5 in) long and is attached to the lateral border of the stomach via the gastroepiploic ligament. The spleen is a fragile organ without a strong capsule, and is dark red due to its extensive vascularization. The spleen is sometimes called the "filter of the blood" because of its extensive vascularization and the presence of macrophages and dendritic cells that remove microbes and other materials from the blood, including dying red blood cells. The spleen also functions as the location of immune responses to blood-borne pathogens.
The spleen is also divided by trabeculae of connective tissue, and within each splenic nodule is an area of red pulp, consisting of mostly red blood cells, and white pulp, which resembles the lymphoid follicles of the lymph nodes. Upon entering the spleen, the splenic artery splits into several arterioles (surrounded by white pulp) and eventually into sinusoids. Blood from the capillaries subsequently collects in the venous sinuses and leaves via the splenic vein. The red pulp consists of reticular fibers with fixed macrophages attached, free macrophages, and all of the other cells typical of the blood, including some lymphocytes. The white pulp surrounds a central arteriole and consists of germinal centers of dividing B cells surrounded by T cells and accessory cells, including macrophages and dendritic cells. Thus, the red pulp primarily functions as a filtration system of the blood, using cells of the relatively nonspecific immune response, and white pulp is where adaptive T and B cell responses are mounted.

**Lymphoid Nodules**

The other lymphoid tissues, the **lymphoid nodules**, have a simpler architecture than the spleen and lymph nodes in that they consist of a dense cluster of lymphocytes without a surrounding fibrous capsule. These nodules are located in the respiratory and digestive tracts, areas routinely exposed to environmental pathogens.
**Tonsils** are lymphoid nodules located along the inner surface of the pharynx and are important in developing immunity to oral pathogens. The tonsil located at the back of the throat, the pharyngeal tonsil, is sometimes referred to as the adenoid when swollen. Such swelling is an indication of an active immune response to infection. Histologically, tonsils do not contain a complete capsule, and the epithelial layer invaginates deeply into the interior of the tonsil to form tonsillar crypts. These structures, which accumulate all sorts of materials taken into the body through eating and breathing, actually “encourage” pathogens to penetrate deep into the tonsillar tissues where they are acted upon by numerous lymphoid follicles and eliminated. This seems to be the major function of tonsils—to help children’s bodies recognize, destroy, and develop immunity to common environmental pathogens so that they will be protected in their later lives. Tonsils are often removed in those children who have recurring throat infections, especially those involving the palatine tonsils on either side of the throat, whose swelling may interfere with their breathing and/or swallowing.

![Diagram of Locations of the Tonsils](image1.png)

![Histology of Palatine Tonsil](image2.png)

**Figure 9.** (a) The pharyngeal tonsil is located on the roof of the posterior superior wall of the nasopharynx. The palatine tonsils lay on each side of the pharynx. (b) A
**Mucosa-associated lymphoid tissue (MALT)** consists of an aggregate of lymphoid follicles directly associated with the mucous membrane epithelia. MALT makes up dome-shaped structures found underlying the mucosa of the gastrointestinal tract, breast tissue, lungs, and eyes. Peyer’s patches, a type of MALT in the small intestine, are especially important for immune responses against ingested substances. Peyer’s patches contain specialized endothelial cells called M (or microfold) cells that sample material from the intestinal lumen and transport it to nearby follicles so that adaptive immune responses to potential pathogens can be mounted.

**Bronchus-associated lymphoid tissue (BALT)** consists of lymphoid follicular structures with an overlying epithelial layer found along the bifurcations of the bronchi, and between bronchi and arteries. They also have the typically less-organized structure of other lymphoid nodules. These tissues, in addition to the tonsils, are effective against inhaled pathogens.

**Chapter Review**

The lymphatic system is a series of vessels, ducts, and trunks that remove interstitial fluid from the tissues and return it the blood. The lymphatics are also used to transport dietary lipids and cells of the immune system. Cells of the immune system all come from the hematopoietic system of the bone marrow. Primary lymphoid organs, the bone marrow and thymus gland, are the locations where lymphocytes of the adaptive immune system proliferate and mature. Secondary lymphoid organs are sites in which mature lymphocytes congregate to mount immune responses. Many immune system cells use the lymphatic and circulatory systems for transport throughout the body to search for and then protect against pathogens.

**Critical Thinking Question**

Describe the flow of lymph from its origins in interstitial fluid to its emptying into the venous bloodstream.
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The Adaptive Immune Response: T lymphocytes and Their Functional Types

Learning Objectives

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

- Explain the advantages of the adaptive immune response over the innate immune response
- List the various characteristics of an antigen
- Describe the types of T cell antigen receptors
- Outline the steps of T cell development
- Describe the major T cell types and their functions

Innate immune responses (and early induced responses) are in many cases ineffective at completely controlling pathogen growth. However, they slow pathogen growth and allow time for the adaptive immune response to strengthen and either control or eliminate the pathogen. The innate immune system also sends signals to the cells of the adaptive immune system, guiding them in how to attack the pathogen. Thus, these are the two important arms of the immune response.

The Benefits of the Adaptive Immune Response

The specificity of the adaptive immune response—its ability to specifically recognize and make a response against a wide variety of pathogens—is its great strength. Antigens, the small chemical groups often associated with pathogens, are recognized by receptors on the surface of B and T lymphocytes. The adaptive immune response to these antigens is so versatile that it can respond to nearly any pathogen. This increase in specificity comes because the adaptive immune response has a unique way to develop as many as $10^{11}$, or 100 trillion, different receptors to recognize nearly every conceivable pathogen. How could so many different types of antibodies be encoded? And what about the many specificities of T cells? There is not nearly enough DNA in a cell to have a separate gene for each specificity. The mechanism was finally worked out in the 1970s and 1980s using the new tools of molecular genetics.

Primary Disease and Immunological Memory

The immune system’s first exposure to a pathogen is called a primary adaptive response. Symptoms of a first infection, called primary disease, are always relatively severe because it takes time for an initial adaptive immune response to a pathogen to become effective.

Upon re-exposure to the same pathogen, a secondary adaptive immune response is generated, which is stronger and faster that the primary response. The secondary adaptive response often eliminates a pathogen before it can cause significant tissue damage or any symptoms. Without symptoms, there is no disease, and the individual is not even aware of the infection. This secondary response is the basis of immunological memory, which protects us from getting diseases repeatedly from the same pathogen. By this mechanism, an individual’s exposure to pathogens early in life spares the person from these diseases later in life.
Self Recognition

A third important feature of the adaptive immune response is its ability to distinguish between self-antigens, those that are normally present in the body, and foreign antigens, those that might be on a potential pathogen. As T and B cells mature, there are mechanisms in place that prevent them from recognizing self-antigen, preventing a damaging immune response against the body. These mechanisms are not 100 percent effective, however, and their breakdown leads to autoimmune diseases, which will be discussed later in this chapter.

T Cell-Mediated Immune Responses

The primary cells that control the adaptive immune response are the lymphocytes, the T and B cells. T cells are particularly important, as they not only control a multitude of immune responses directly, but also control B cell immune responses in many cases as well. Thus, many of the decisions about how to attack a pathogen are made at the T cell level, and knowledge of their functional types is crucial to understanding the functioning and regulation of adaptive immune responses as a whole.

T lymphocytes recognize antigens based on a two-chain protein receptor. The most common and important of these are the alpha-beta T cell receptors (Figure 1).

There are two chains in the T cell receptor, and each chain consists of two domains. The variable region domain is furthest away from the T cell membrane and is so named because its amino acid sequence varies between receptors. In contrast, the constant region domain has less variation. The differences in the amino acid sequences of the variable domains are the molecular basis of the diversity of antigens the receptor can recognize. Thus, the antigen-binding site of the receptor consists of the terminal ends of both receptor chains, and the amino acid sequences of those two areas combine to determine its antigenic specificity. Each T cell produces only one type of receptor and thus is specific for a single particular antigen.

Antigens

Antigens on pathogens are usually large and complex, and consist of many antigenic determinants. An antigenic determinant (epitope) is one of the small regions within an antigen to which a receptor can bind, and antigenic determinants are limited by the size of the receptor itself. They usually consist of six or fewer amino acid residues in a protein, or one or two sugar moieties in a carbohydrate antigen. Antigenic determinants on a carbohydrate antigen are usually less diverse than on a protein antigen. Carbohydrate antigens are found on bacterial cell walls and on red blood cells (the ABO blood group antigens). Protein antigens are complex because of the variety of three-dimensional shapes that proteins can assume, and are especially important for the immune responses to viruses and worm parasites. It is the interaction of the shape of the antigen and the complementary shape of the amino acids of the antigen-binding site that accounts for the chemical basis of specificity.
Antigen Processing and Presentation

Although Figure 2 shows T cell receptors interacting with antigenic determinants directly, the mechanism that T cells use to recognize antigens is, in reality, much more complex. T cells do not recognize free-floating or cell-bound antigens as they appear on the surface of the pathogen. They only recognize antigen on the surface of specialized cells called antigen-presenting cells. Antigens are internalized by these cells.

**Antigen processing** is a mechanism that enzymatically cleaves the antigen into smaller pieces. The antigen fragments are then brought to the cell’s surface and associated with a specialized type of antigen-presenting protein known as a **major histocompatibility complex (MHC)** molecule. The MHC is the cluster of genes that encode these antigen-presenting molecules. The association of the antigen fragments with an MHC molecule on the surface of a cell is known as **antigen presentation** and results in the recognition of antigen by a T cell. This association of antigen and MHC occurs inside the cell, and it is the complex of the two that is brought to the surface. The peptide-binding cleft is a small indentation at the end of the MHC molecule that is furthest away from the cell membrane; it is here that the processed fragment of antigen sits. MHC molecules are capable of presenting a variety of antigens, depending on the amino acid sequence, in their peptide-binding clefts. It is the combination of the MHC molecule and the fragment of the original peptide or carbohydrate that is actually physically recognized by the T cell receptor.
Two distinct types of MHC molecules, **MHC class I** and **MHC class II**, play roles in antigen presentation. Although produced from different genes, they both have similar functions. They bring processed antigen to the surface of the cell via a transport vesicle and present the antigen to the T cell and its receptor. Antigens from different classes of pathogens, however, use different MHC classes and take different routes through the cell to get to the surface for presentation. The basic mechanism, though, is the same. Antigens are processed by digestion, are brought into the endomembrane system of the cell, and then are expressed on the surface of the antigen-presenting cell for antigen recognition by a T cell. Intracellular antigens are typical of viruses, which replicate inside the cell, and certain other intracellular parasites and bacteria. These antigens are processed in the cytosol by an enzyme complex known as the proteasome and are then brought into the endoplasmic reticulum by the transporter associated with antigen processing (TAP) system, where they interact with class I MHC molecules and are eventually transported to the cell surface by a transport vesicle.

Extracellular antigens, characteristic of many bacteria, parasites, and fungi that do not replicate inside the cell’s cytoplasm, are brought into the endomembrane system of the cell by receptor-mediated endocytosis. The resulting vesicle fuses with vesicles from the Golgi complex, which contain pre-formed MHC class II molecules. After fusion of these two vesicles and the association of antigen and MHC, the new vesicle makes its way to the cell surface.

**Professional Antigen-presenting Cells**

Many cell types express class I molecules for the presentation of intracellular antigens. These MHC molecules may then stimulate a cytotoxic T cell immune response, eventually destroying the cell and the pathogen within. This is especially important when it comes to the most common class of intracellular pathogens, the virus. Viruses infect nearly every tissue of the body, so all these tissues must necessarily be able to express class I MHC or no T cell response can be made.

On the other hand, class II MHC molecules are expressed only on the cells of the immune system, specifically cells that affect other arms of the immune response. Thus, these cells are called “professional” antigen-presenting cells to distinguish them from those that bear class I MHC. The three types of professional antigen presenters are macrophages, dendritic cells, and B cells.
Macrophages stimulate T cells to release cytokines that enhance phagocytosis. Dendritic cells also kill pathogens by phagocytosis, but their major function is to bring antigens to regional draining lymph nodes. The lymph nodes are the locations in which most T cell responses against pathogens of the interstitial tissues are mounted. Macrophages are found in the skin and in the lining of mucosal surfaces, such as the nasopharynx, stomach, lungs, and intestines. B cells may also present antigens to T cells, which are necessary for certain types of antibody responses, to be covered later in this chapter.

<table>
<thead>
<tr>
<th>MHC</th>
<th>Cell type</th>
<th>Phagocytic?</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Many</td>
<td>No</td>
<td>Stimulates cytotoxic T cell immune response</td>
</tr>
<tr>
<td>Class II</td>
<td>Macrophage</td>
<td>Yes</td>
<td>Stimulates phagocytosis and presentation at primary infection site</td>
</tr>
<tr>
<td>Class II</td>
<td>Dendritic</td>
<td>Yes, in tissues</td>
<td>Brings antigens to regional lymph nodes</td>
</tr>
<tr>
<td>Class II</td>
<td>B cell</td>
<td>Yes, internalizes surface Ig and antigen</td>
<td>Stimulates antibody secretion by B cells</td>
</tr>
</tbody>
</table>

**T Cell Development and Differentiation**

The process of eliminating T cells that might attack the cells of one’s own body is referred to as **T cell tolerance**. While thymocytes are in the cortex of the thymus, they are referred to as “double negatives,” meaning that they do not bear the CD4 or CD8 molecules that you can use to follow their pathways of differentiation. In the cortex of the thymus, they are exposed to cortical epithelial cells. In a process known as **positive selection**, double-negative thymocytes bind to the MHC molecules they observe on the thymic epithelia, and the MHC molecules of “self” are selected. This mechanism kills many thymocytes during T cell differentiation. In fact, only two percent of the thymocytes that enter the thymus leave it as mature, functional T cells.
Figure 4. Click to view a larger image. Thymocytes enter the thymus and go through a series of developmental stages that ensures both function and tolerance before they leave and become functional components of the adaptive immune response.

Later, the cells become double positives that express both CD4 and CD8 markers and move from the cortex to the junction between the cortex and medulla. It is here that negative selection takes place. In negative selection, self-antigens are brought into the thymus from other parts of the body by professional antigen-presenting cells. The T cells that bind to these self-antigens are selected for negatively and are killed by apoptosis. In summary, the only T cells left are those that can bind to MHC molecules of the body with foreign antigens presented on their binding clefts, preventing an attack on one's own body tissues, at least under normal circumstances. Tolerance can be broken, however, by the development of an autoimmune response, to be discussed later in this chapter.

The cells that leave the thymus become single positives, expressing either CD4 or CD8, but not both. The CD4⁺ T cells will bind to class II MHC and the CD8⁺ cells will bind to class I MHC. The discussion that follows explains the functions of these molecules and how they can be used to differentiate between the different T cell functional types.
Mechanisms of T Cell-mediated Immune Responses

Mature T cells become activated by recognizing processed foreign antigen in association with a self-MHC molecule and begin dividing rapidly by mitosis. This proliferation of T cells is called clonal expansion and is necessary to make the immune response strong enough to effectively control a pathogen. How does the body select only those T cells that are needed against a specific pathogen? Again, the specificity of a T cell is based on the amino acid sequence and the three-dimensional shape of the antigen-binding site formed by the variable regions of the two chains of the T cell receptor. Clonal selection is the process of antigen binding only to those T cells that have receptors specific to that antigen. Each T cell that is activated has a specific receptor “hard-wired” into its DNA, and all of its progeny will have identical DNA and T cell receptors, forming clones of the original T cell.

Clonal Selection and Expansion

The clonal selection theory was proposed by Frank Burnet in the 1950s. However, the term clonal selection is not a complete description of the theory, as clonal expansion goes hand in glove with the selection process. The main tenet of the theory is that a typical individual has a multitude ($10^{11}$) of different types of T cell clones based on
their receptors. In this use, a **clone** is a group of lymphocytes that share the same **antigen receptor**. Each clone is necessarily present in the body in low numbers. Otherwise, the body would not have room for lymphocytes with so many specificities.

Only those clones of lymphocytes whose receptors are activated by the antigen are stimulated to proliferate. Keep in mind that most antigens have multiple antigenic determinants, so a T cell response to a typical antigen involves a polyclonal response. A **polyclonal response** is the stimulation of multiple T cell clones. Once activated, the selected clones increase in number and make many copies of each cell type, each clone with its unique receptor. By the time this process is complete, the body will have large numbers of specific lymphocytes available to fight the infection.

### The Cellular Basis of Immunological Memory

As already discussed, one of the major features of an adaptive immune response is the development of immunological memory.

During a primary adaptive immune response, both **memory T cells** and **effector T cells** are generated. Memory T cells are long-lived and can even persist for a lifetime. Memory cells are primed to act rapidly. Thus, any subsequent exposure to the pathogen will elicit a very rapid T cell response. This rapid, secondary adaptive response generates large numbers of effector T cells so fast that the pathogen is often overwhelmed before it can cause any symptoms of disease. This is what is meant by immunity to a disease. The same pattern of primary and secondary immune responses occurs in B cells and the antibody response, as will be discussed later in the chapter.

### T Cell Types and their Functions

In the discussion of T cell development, you saw that mature T cells express either the CD4 marker or the CD8 marker, but not both. These markers are cell adhesion molecules that keep the T cell in close contact with the antigen-presenting cell by directly binding to the MHC molecule (to a different part of the molecule than does the antigen). Thus, T cells and antigen-presenting cells are held together in two ways: by CD4 or CD8 attaching to MHC and by the T cell receptor binding to antigen.
Figure 6. (a) CD4 is associated with helper and regulatory T cells. An extracellular pathogen is processed and presented in the binding cleft of a class II MHC molecule, and this interaction is strengthened by the CD4 molecule. (b) CD8 is associated with cytotoxic T cells. An intracellular pathogen is presented by a class I MHC molecule, and CD8 interacts with it.

Although the correlation is not 100 percent, CD4-bearing T cells are associated with helper functions and CD8-bearing T cells are associated with cytotoxicity. These functional distinctions based on CD4 and CD8 markers are useful in defining the function of each type.

**Helper T Cells and their Cytokines**

**Helper T cells (Th),** bearing the CD4 molecule, function by secreting cytokines that act to enhance other immune responses. There are two classes of Th cells, and they act on different components of the immune response. These cells are not distinguished by their surface molecules but by the characteristic set of cytokines they secrete.

- **Th1 cells** are a type of helper T cell that secretes cytokines that regulate the immunological activity and development of a variety of cells, including macrophages and other types of T cells.
- **Th2 cells,** on the other hand, are cytokine-secreting cells that act on B cells to drive their differentiation into plasma cells that make antibody. In fact, T cell help is required for antibody responses to most protein antigens, and these are called T cell-dependent antigens.
Cytotoxic T cells

Cytotoxic T cells (Tc) are T cells that kill target cells by inducing apoptosis using the same mechanism as NK cells. They either express Fas ligand, which binds to the fas molecule on the target cell, or act by using perforins and granzymes contained in their cytoplasmic granules. As was discussed earlier with NK cells, killing a virally infected cell before the virus can complete its replication cycle results in the production of no infectious particles. As more Tc cells are developed during an immune response, they overwhelm the ability of the virus to cause disease. In addition, each Tc cell can kill more than one target cell, making them especially effective. Tc cells are so important in the antiviral immune response that some speculate that this was the main reason the adaptive immune response evolved in the first place.

Regulatory T Cells

Regulatory T cells (Treg), or suppressor T cells, are the most recently discovered of the types listed here, so less is understood about them. In addition to CD4, they bear the molecules CD25 and FOXP3. Exactly how they function is still under investigation, but it is known that they suppress other T cell immune responses. This is an important feature of the immune response, because if clonal expansion during immune responses were allowed to continue uncontrolled, these responses could lead to autoimmune diseases and other medical issues.

Not only do T cells directly destroy pathogens, but they regulate nearly all other types of the adaptive immune response as well, as evidenced by the functions of the T cell types, their surface markers, the cells they work on, and the types of pathogens they work against.

<table>
<thead>
<tr>
<th>T cell</th>
<th>Main target</th>
<th>Function</th>
<th>Pathogen</th>
<th>Surface marker</th>
<th>MHC</th>
<th>Cytokines or mediators</th>
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<tr>
<td>Tc</td>
<td>Infected cells</td>
<td>Cytotoxicity</td>
<td>Intracellular</td>
<td>CD8</td>
<td>Class I</td>
<td>Perforins, granzymes, and fas ligand</td>
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<tr>
<td>Th1</td>
<td>Macrophage</td>
<td>Helper inducer</td>
<td>Extracellular</td>
<td>CD4</td>
<td>Class II</td>
<td>Interferon-γ and TGF-β</td>
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<tr>
<td>Th2</td>
<td>B cell</td>
<td>Helper inducer</td>
<td>Extracellular</td>
<td>CD4</td>
<td>Class II</td>
<td>IL-4, IL-6, IL-10, and others</td>
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<tr>
<td>Treg</td>
<td>Th cell</td>
<td>Suppressor</td>
<td>None</td>
<td>CD4, CD25</td>
<td>?</td>
<td>TGF-β and IL-10</td>
</tr>
</tbody>
</table>

Chapter Review

T cells recognize antigens with their antigen receptor, a complex of two protein chains on their surface. They do not recognize self-antigens, however, but only processed antigen presented on their surfaces in a binding groove of a major histocompatibility complex molecule. T cells develop in the thymus, where they learn to use self-MHC molecules to recognize only foreign antigens, thus making them tolerant to self-antigens. There are several functional types of T lymphocytes, the major ones being helper, regulatory, and cytotoxic T cells.

Critical Thinking Questions

Describe the processing and presentation of an intracellular antigen.
Describe clonal selection and expansion.
The Adaptive Immune Response: B-lymphocytes and Antibodies

Learning Objectives

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

- Explain how B cells mature and how B cell tolerance develops
- Discuss how B cells are activated and differentiate into plasma cells
- Describe the structure of the antibody classes and their functions

Antibodies were the first component of the adaptive immune response to be characterized by scientists working on the immune system. It was already known that individuals who survived a bacterial infection were immune to re-infection with the same pathogen. Early microbiologists took serum from an immune patient and mixed it with a fresh culture of the same type of bacteria, then observed the bacteria under a microscope. The bacteria became clumped in a process called agglutination. When a different bacterial species was used, the agglutination did not happen. Thus, there was something in the serum of immune individuals that could specifically bind to and agglutinate bacteria.

Scientists now know the cause of the agglutination is an antibody molecule, also called an immunoglobulin. What is an antibody? An antibody protein is essentially a secreted form of a B cell receptor. (In fact, surface immunoglobulin is another name for the B cell receptor.) Not surprisingly, the same genes encode both the secreted antibodies and the surface immunoglobulins. One minor difference in the way these proteins are synthesized distinguishes a naïve B cell with antibody on its surface from an antibody-secreting plasma cell with no antibodies on its surface. The antibodies of the plasma cell have the exact same antigen-binding site and specificity as their B cell precursors.

There are five different classes of antibody found in humans: IgM, IgD, IgG, IgA, and IgE. Each of these has specific functions in the immune response, so by learning about them, researchers can learn about the great variety of antibody functions critical to many adaptive immune responses.

B cells do not recognize antigen in the complex fashion of T cells. B cells can recognize native, unprocessed antigen and do not require the participation of MHC molecules and antigen-presenting cells.

B Cell Differentiation and Activation

B cells differentiate in the bone marrow. During the process of maturation, up to 100 trillion different clones of B cells are generated, which is similar to the diversity of antigen receptors seen in T cells.

B cell differentiation and the development of tolerance are not quite as well understood as it is in T cells. Central tolerance is the destruction or inactivation of B cells that recognize self-antigens in the bone marrow, and its role is critical and well established. In the process of clonal deletion, immature B cells that bind strongly to self-antigens expressed on tissues are signaled to commit suicide by apoptosis, removing them from the population. In the process of clonal anergy, however, B cells exposed to soluble antigen in the bone marrow are not physically deleted, but become unable to function.

Another mechanism called peripheral tolerance is a direct result of T cell tolerance. In peripheral tolerance,
functional, mature B cells leave the bone marrow but have yet to be exposed to self-antigen. Most protein antigens require signals from helper T cells (Th2) to proceed to make antibody. When a B cell binds to a self-antigen but receives no signals from a nearby Th2 cell to produce antibody, the cell is signaled to undergo apoptosis and is destroyed. This is yet another example of the control that T cells have over the adaptive immune response.

After B cells are activated by their binding to antigen, they differentiate into plasma cells. Plasma cells often leave the secondary lymphoid organs, where the response is generated, and migrate back to the bone marrow, where the whole differentiation process started. After secreting antibodies for a specific period, they die, as most of their energy is devoted to making antibodies and not to maintaining themselves. Thus, plasma cells are said to be terminally differentiated.

The final B cell of interest is the memory B cell, which results from the clonal expansion of an activated B cell. Memory B cells function in a way similar to memory T cells. They lead to a stronger and faster secondary response when compared to the primary response, as illustrated below.

### Antibody Structure

Antibodies are glycoproteins consisting of two types of polypeptide chains with attached carbohydrates. The **heavy chain** and the **light chain** are the two polypeptides that form the antibody. The main differences between the classes of antibodies are in the differences between their heavy chains, but as you shall see, the light chains have an important role, forming part of the antigen-binding site on the antibody molecules.

#### Four-chain Models of Antibody Structures

All antibody molecules have two identical heavy chains and two identical light chains. (Some antibodies contain multiple units of this four-chain structure.) The **Fc region** of the antibody is formed by the two heavy chains coming together, usually linked by disulfide bonds. The Fc portion of the antibody is important in that many effector cells of the immune system have Fc receptors. Cells having these receptors can then bind to antibody-coated pathogens, greatly increasing the specificity of the effector cells. At the other end of the molecule are two identical antigen-binding sites.

![Antibody Structure Diagram](credit b: modification of work by Tim Vickers)

#### Five Classes of Antibodies and their Functions

In general, antibodies have two basic functions. They can act as the B cell antigen receptor or they can be secreted, circulate, and bind to a pathogen, often labeling it for identification by other forms of the immune response. Of the five antibody classes, notice that only two can function as the antigen receptor for naïve B cells: IgM and **IgD** (see Table 1). Mature B cells that leave the bone marrow express both IgM and IgD, but both
antibodies have the same antigen specificity. Only IgM is secreted, however, and no other nonreceptor function for IgD has been discovered.

### Table 1. The Five Immunoglobulin (Ig) Classes

<table>
<thead>
<tr>
<th></th>
<th>IgM pentamer</th>
<th>IgG monomer</th>
<th>Secretory IgA dimer</th>
<th>IgE monomer</th>
<th>IgD monomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy Chains</td>
<td>μ</td>
<td>γ</td>
<td>α</td>
<td>ε</td>
<td>δ</td>
</tr>
<tr>
<td>Number of antigen binding sites</td>
<td>10</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Molecular weight (Daltons)</td>
<td>900,000</td>
<td>150,000</td>
<td>385,000</td>
<td>200,000</td>
<td>180,000</td>
</tr>
<tr>
<td>Percentage of total antibody in serum</td>
<td>6%</td>
<td>80%</td>
<td>13%</td>
<td>0.002%</td>
<td>1%</td>
</tr>
<tr>
<td>Crosses placenta</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Fixes complement</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Fc binds to</td>
<td>plasmocytes</td>
<td>mast cells and basophils</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td>Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor</td>
<td>Main blood antibody of secondary responses, neutralizes toxins, opsonization</td>
<td>Secreted into mucus, tears, saliva, colostrum</td>
<td>Antibody of allergy and antiparasitic activity</td>
<td>B cell receptor</td>
</tr>
</tbody>
</table>

**IgM** consists of five four-chain structures (20 total chains with 10 identical antigen-binding sites) and is thus the largest of the antibody molecules. IgM is usually the first antibody made during a primary response. Its 10 antigen-binding sites and large shape allow it to bind well to many bacterial surfaces. It is excellent at binding complement proteins and activating the complement cascade, consistent with its role in promoting chemotaxis, opsonization, and cell lysis. Thus, it is a very effective antibody against bacteria at early stages of a primary antibody response. As the primary response proceeds, the antibody produced in a B cell can change to IgG, IgA, or IgE by the process known as class switching. **Class switching** is the change of one antibody class to another. While the class of antibody changes, the specificity and the antigen-binding sites do not. Thus, the antibodies made are still specific to the pathogen that stimulated the initial IgM response.

**IgG** is a major antibody of late primary responses and the main antibody of secondary responses in the blood. This is because class switching occurs during primary responses. IgG is a monomeric antibody that clears pathogens from the blood and can activate complement proteins (although not as well as IgM), taking advantage of its antibacterial activities. Furthermore, this class of antibody is the one that crosses the placenta to protect the developing fetus from disease exits the blood to the interstitial fluid to fight extracellular pathogens.

**IgA** exists in two forms, a four-chain monomer in the blood and an eight-chain structure, or dimer, in exocrine gland secretions of the mucous membranes, including mucus, saliva, and tears. Thus, dimeric IgA is the only antibody to leave the interior of the body to protect body surfaces. IgA is also of importance to newborns, because this antibody is present in mother’s breast milk (colostrum), which serves to protect the infant from disease.

**IgE** is usually associated with allergies and anaphylaxis. It is present in the lowest concentration in the blood, because its Fc region binds strongly to an IgE-specific Fc receptor on the surfaces of mast cells. IgE makes mast cell degranulation very specific, such that if a person is allergic to peanuts, there will be peanut-specific IgE bound to his or her mast cells. In this person, eating peanuts will cause the mast cells to degranulate, sometimes causing severe allergic reactions, including anaphylaxis, a severe, systemic allergic response that can cause death.

### Clonal Selection of B Cells

Clonal selection and expansion work much the same way in B cells as in T cells. Only B cells with appropriate antigen specificity are selected for and expanded. Eventually, the plasma cells secrete antibodies with antigenic specificity identical to those that were on the surfaces of the selected B cells. Notice in the figure that both plasma cells and memory B cells are generated simultaneously.
Primary versus Secondary B Cell Responses

Primary and secondary responses as they relate to T cells were discussed earlier. This section will look at these responses with B cells and antibody production. Because antibodies are easily obtained from blood samples, they are easy to follow and graph (Figure 3). As you will see from the figure, the primary response to an antigen (representing a pathogen) is delayed by several days. This is the time it takes for the B cell clones to expand and differentiate into plasma cells. The level of antibody produced is low, but it is sufficient for immune protection. The second time a person encounters the same antigen, there is no time delay, and the amount of antibody made is much higher. Thus, the secondary antibody response overwhelms the pathogens quickly and, in most situations, no symptoms are felt. When a different antigen is used, another primary response is made with its low antibody levels and time delay.

Figure 2. During a primary B cell immune response, both antibody-secreting plasma cells and memory B cells are produced. These memory cells lead to the differentiation of more plasma cells and memory B cells during secondary responses.
Figure 3. Antigen A is given once to generate a primary response and later to generate a secondary response. When a different antigen is given for the first time, a new primary response is made.

Active versus Passive Immunity

Immunity to pathogens, and the ability to control pathogen growth so that damage to the tissues of the body is limited, can be acquired by (1) the active development of an immune response in the infected individual or (2) the passive transfer of immune components from an immune individual to a nonimmune one. Both active and passive immunity have examples in the natural world and as part of medicine.

**Active immunity** is the resistance to pathogens acquired during an adaptive immune response within an individual. Naturally acquired active immunity, the response to a pathogen, is the focus of this chapter. Artificially acquired active immunity involves the use of vaccines. A vaccine is a killed or weakened pathogen or its components that, when administered to a healthy individual, leads to the development of immunological memory (a weakened primary immune response) without causing much in the way of symptoms. Thus, with the use of vaccines, one can avoid the damage from disease that results from the first exposure to the pathogen, yet reap the benefits of protection from immunological memory. The advent of vaccines was one of the major medical advances of the twentieth century and led to the eradication of smallpox and the control of many infectious diseases, including polio, measles, and whooping cough.

<table>
<thead>
<tr>
<th></th>
<th>Natural</th>
<th>Artificial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active</strong></td>
<td>Adaptive immune response</td>
<td>Vaccine response</td>
</tr>
<tr>
<td><strong>Passive</strong></td>
<td>Trans-placental antibodies/breastfeeding</td>
<td>Immune globulin injections</td>
</tr>
</tbody>
</table>

**Passive immunity** arises from the transfer of antibodies to an individual without requiring them to mount their own active immune response. Naturally acquired passive immunity is seen during fetal development. IgG is transferred from the maternal circulation to the fetus via the placenta, protecting the fetus from infection and protecting the newborn for the first few months of its life. As already stated, a newborn benefits from the IgA antibodies it obtains from milk during breastfeeding. The fetus and newborn thus benefit from the immunological...
memory of the mother to the pathogens to which she has been exposed. In medicine, artificially acquired passive immunity usually involves injections of immunoglobulins, taken from animals previously exposed to a specific pathogen. This treatment is a fast-acting method of temporarily protecting an individual who was possibly exposed to a pathogen. The downside to both types of passive immunity is the lack of the development of immunological memory. Once the antibodies are transferred, they are effective for only a limited time before they degrade.

Practice Questions

Immunity can be acquired in an active or passive way, and it can be natural or artificial. Watch this video to see an animated discussion of passive and active immunity. What is an example of natural immunity acquired passively?
Show Answer

T cell-dependent versus T cell-independent Antigens

As discussed previously, Th2 cells secrete cytokines that drive the production of antibodies in a B cell, responding to complex antigens such as those made by proteins. On the other hand, some antigens are T cell independent. A T cell-independent antigen usually is in the form of repeated carbohydrate moieties found on the cell walls of bacteria. Each antibody on the B cell surface has two binding sites, and the repeated nature of T cell-independent antigen leads to crosslinking of the surface antibodies on the B cell. The crosslinking is enough to activate it in the absence of T cell cytokines.

A T cell-dependent antigen, on the other hand, usually is not repeated to the same degree on the pathogen and thus does not crosslink surface antibody with the same efficiency. To elicit a response to such antigens, the B and T cells must come close together. The B cell must receive two signals to become activated. Its surface immunoglobulin must recognize native antigen. Some of this antigen is internalized, processed, and presented to the Th2 cells on a class II MHC molecule. The T cell then binds using its antigen receptor and is activated to secrete cytokines that diffuse to the B cell, finally activating it completely. Thus, the B cell receives signals from both its surface antibody and the T cell via its cytokines, and acts as a professional antigen-presenting cell in the process.

Figure 4: To elicit a response to a T cell-dependent antigen, the B and T cells must come close together. To become fully activated, the B cell must receive two signals from the native antigen and the T cell’s cytokines.
Chapter Review

B cells, which develop within the bone marrow, are responsible for making five different classes of antibodies, each with its own functions. B cells have their own mechanisms for tolerance, but in peripheral tolerance, the B cells that leave the bone marrow remain inactive due to T cell tolerance. Some B cells do not need T cell cytokines to make antibody, and they bypass this need by the crosslinking of their surface immunoglobulin by repeated carbohydrate residues found in the cell walls of many bacterial species. Others require T cells to become activated.

Critical Thinking Questions

Describe how secondary B cell responses are developed.
Describe the role of IgM in immunity.

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Diseases Associated with Depressed or Overactive Immune Responses

Learning Objectives

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

- Discuss inherited and acquired immunodeficiencies
- Explain the four types of hypersensitivity and how they differ
- Give an example of how autoimmune disease breaks tolerance

This section is about how the immune system goes wrong. When it goes haywire, and becomes too weak or too strong, it leads to a state of disease. The factors that maintain immunological homeostasis are complex and incompletely understood.

Immunodeficiencies

As you have seen, the immune system is quite complex. It has many pathways using many cell types and signals. Because it is so complex, there are many ways for it to go wrong. Inherited immunodeficiencies arise from gene mutations that affect specific components of the immune response. There are also acquired immunodeficiencies with potentially devastating effects on the immune system, such as HIV.

Inherited Immunodeficiencies

A list of all inherited immunodeficiencies is well beyond the scope of this book. The list is almost as long as the list of cells, proteins, and signaling molecules of the immune system itself. Some deficiencies, such as those for complement, cause only a higher susceptibility to some Gram-negative bacteria. Others are more severe in their consequences. Certainly, the most serious of the inherited immunodeficiencies is severe combined immunodeficiency disease (SCID). This disease is complex because it is caused by many different genetic defects. What groups them together is the fact that both the B cell and T cell arms of the adaptive immune response are affected.

Children with this disease usually die of opportunistic infections within their first year of life unless they receive a bone marrow transplant. Such a procedure had not yet been perfected for David Vetter, the “boy in the bubble,” who was treated for SCID by having to live almost his entire life in a sterile plastic cocoon for the 12 years before his death from infection in 1984. One of the features that make bone marrow transplants work as well as they do is the proliferative capability of hematopoietic stem cells of the bone marrow. Only a small amount of bone marrow from a healthy donor is given intravenously to the recipient. It finds its own way to the bone where it populates it, eventually reconstituting the patient’s immune system, which is usually destroyed beforehand by treatment with radiation or chemotherapeutic drugs.

New treatments for SCID using gene therapy, inserting nondefective genes into cells taken from the patient and giving them back, have the advantage of not needing the tissue match required for standard transplants. Although not a standard treatment, this approach holds promise, especially for those in whom standard bone marrow transplantation has failed.
Human Immunodeficiency Virus/AIDS

Although many viruses cause suppression of the immune system, only one wipes it out completely, and that is the previously mentioned HIV. It is worth discussing the biology of this virus, which can lead to the well-known AIDS, so that its full effects on the immune system can be understood. The virus is transmitted through semen, vaginal fluids, and blood, and can be caught by risky sexual behaviors and the sharing of needles by intravenous drug users. There are sometimes, but not always, flu-like symptoms in the first 1 to 2 weeks after infection. This is later followed by seroconversion. The anti-HIV antibodies formed during seroconversion are the basis for most initial HIV screening done in the United States. Because seroconversion takes different lengths of time in different individuals, multiple AIDS tests are given months apart to confirm or eliminate the possibility of infection.

After seroconversion, the amount of virus circulating in the blood drops and stays at a low level for several years. During this time, the levels of CD4+ cells, especially helper T cells, decline steadily, until at some point, the immune response is so weak that opportunistic disease and eventually death result. CD4 is the receptor that HIV uses to get inside T cells and reproduce. Given that CD4+ helper T cells play an important role in other in T cell immune responses and antibody responses, it should be no surprise that both types of immune responses are eventually seriously compromised.

Treatment for the disease consists of drugs that target virally encoded proteins that are necessary for viral replication but are absent from normal human cells. By targeting the virus itself and sparing the cells, this approach has been successful in significantly prolonging the lives of HIV-positive individuals. On the other hand, an HIV vaccine has been 30 years in development and is still years away. Because the virus mutates rapidly to evade the immune system, scientists have been looking for parts of the virus that do not change and thus would be good targets for a vaccine candidate.

Hypersensitivities

The word “hypersensitivity” simply means sensitive beyond normal levels of activation. Allergies and inflammatory responses to nonpathogenic environmental substances have been observed since the dawn of history. Hypersensitivity is a medical term describing symptoms that are now known to be caused by unrelated mechanisms of immunity. Still, it is useful for this discussion to use the four types of hypersensitivities as a guide to understand these mechanisms. Figure 1 and Table 1 provide an overview of four types of hypersensitivity:

![Figure 1. Four types of hypersensitivity.](image)
Table 1. Components of the immune system cause four types of hypersensitivity.

<table>
<thead>
<tr>
<th>Type I: IgE-Mediated Hypersensitivity</th>
<th>Type II: IgG-Mediated Cytotoxic Hypersensitivity</th>
<th>Type III: Immune Complex-Mediated Hypersensitivity</th>
<th>Type IV: Cell-Mediated Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.</td>
<td>Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC).</td>
<td>Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site.</td>
<td>Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site.</td>
</tr>
<tr>
<td>Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema.</td>
<td>Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood types or during erythroblastosis fetalis</td>
<td>Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.</td>
<td>Most common forms are contact dermatitis, tuberculin reaction, and autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis.</td>
</tr>
</tbody>
</table>

Notice that types I–III are B cell mediated, whereas type IV hypersensitivity is exclusively a T cell phenomenon.

Immediate (Type I) Hypersensitivity

Antigens that cause allergic responses are often referred to as allergens. The specificity of the immediate hypersensitivity response is predicated on the binding of allergen-specific IgE to the mast cell surface. The process of producing allergen-specific IgE is called sensitization, and is a necessary prerequisite for the symptoms of immediate hypersensitivity to occur. Allergies and allergic asthma are mediated by mast cell degranulation that is caused by the crosslinking of the antigen-specific IgE molecules on the mast cell surface. The mediators released have various vasoactive effects already discussed, but the major symptoms of inhaled allergens are the nasal edema and runny nose caused by the increased vascular permeability and increased blood flow of nasal blood vessels. As these mediators are released with mast cell degranulation, type I hypersensitivity reactions are usually rapid and occur within just a few minutes, hence the term immediate hypersensitivity.

Most allergens are in themselves nonpathogenic and therefore innocuous. Some individuals develop mild allergies, which are usually treated with antihistamines. Others develop severe allergies that may cause anaphylactic shock, which can potentially be fatal within 20 to 30 minutes if untreated. This drop in blood pressure (shock) with accompanying contractions of bronchial smooth muscle is caused by systemic mast cell degranulation when an allergen is eaten (for example, shellfish and peanuts), injected (by a bee sting or being administered penicillin), or inhaled (asthma). Because epinephrine raises blood pressure and relaxes bronchial smooth muscle, it is routinely used to counteract the effects of anaphylaxis and can be lifesaving. Patients with known severe allergies are encouraged to keep automatic epinephrine injectors with them at all times, especially when away from easy access to hospitals.

Allergists use skin testing to identify allergens in type I hypersensitivity. In skin testing, allergen extracts are injected into the epidermis, and a positive result of a soft, pale swelling at the site surrounded by a red zone (called the wheal and flare response), caused by the release of histamine and the granule mediators, usually occurs within 30 minutes. The soft center is due to fluid leaking from the blood vessels and the redness is caused by the increased blood flow to the area that results from the dilation of local blood vessels at the site.

Type II and Type III Hypersensitivities

**Type II hypersensitivity**, which involves IgG-mediated lysis of cells by complement proteins, occurs during mismatched blood transfusions and blood compatibility diseases such as erythroblastosis fetalis (see section on transplantation). **Type III hypersensitivity** occurs with diseases such as systemic lupus erythematosus, where soluble antigens, mostly DNA and other material from the nucleus, and antibodies accumulate in the blood to the point that the antigen and antibody precipitate along blood vessel linings. These immune complexes often lodge in the kidneys, joints, and other organs where they can activate complement proteins and cause inflammation.
Delayed (Type IV) Hypersensitivity

Delayed hypersensitivity, or type IV hypersensitivity, is basically a standard cellular immune response. In delayed hypersensitivity, the first exposure to an antigen is called sensitization, such that on re-exposure, a secondary cellular response results, secreting cytokines that recruit macrophages and other phagocytes to the site. These sensitized T cells, of the Th1 class, will also activate cytotoxic T cells. The time it takes for this reaction to occur accounts for the 24- to 72-hour delay in development.

The classical test for delayed hypersensitivity is the tuberculin test for tuberculosis, where bacterial proteins from *M. tuberculosis* are injected into the skin. A couple of days later, a positive test is indicated by a raised red area that is hard to the touch, called an induration, which is a consequence of the cellular infiltrate, an accumulation of activated macrophages. A positive tuberculin test means that the patient has been exposed to the bacteria and exhibits a cellular immune response to it.

Another type of delayed hypersensitivity is contact sensitivity, where substances such as the metal nickel cause a red and swollen area upon contact with the skin. The individual must have been previously sensitized to the metal. A much more severe case of contact sensitivity is poison ivy, but many of the harshest symptoms of the reaction are associated with the toxicity of its oils and are not T cell mediated.

Autoimmune Responses

The worst cases of the immune system over-reacting are autoimmune diseases. Somehow, tolerance breaks down and the immune systems in individuals with these diseases begin to attack their own bodies, causing significant damage. The trigger for these diseases is, more often than not, unknown, and the treatments are usually based on resolving the symptoms using immunosuppressive and anti-inflammatory drugs such as steroids. These diseases can be localized and crippling, as in rheumatoid arthritis, or diffuse in the body with multiple symptoms that differ in different individuals, as is the case with systemic lupus erythematosus.

Environmental triggers seem to play large roles in autoimmune responses. One explanation for the breakdown of tolerance is that, after certain bacterial infections, an immune response to a component of the bacterium cross-reacts with a self-antigen. This mechanism is seen in rheumatic fever, a result of infection with *Streptococcus* bacteria, which causes strep throat. The antibodies to this pathogen’s M protein cross-react with an antigenic component of heart myosin, a major contractile protein of the heart that is critical to its normal function. The antibody binds to these molecules and activates complement proteins, causing damage to the heart, especially to the heart valves. On the other hand, some theories propose that having multiple common infectious diseases
Anatomy

actually prevents autoimmune responses. The fact that autoimmune diseases are rare in countries that have a high incidence of infectious diseases supports this idea, another example of the hygiene hypothesis discussed earlier in this chapter.

There are genetic factors in autoimmune diseases as well. Some diseases are associated with the MHC genes that an individual expresses. The reason for this association is likely because if one’s MHC molecules are not able to present a certain self-antigen, then that particular autoimmune disease cannot occur. Overall, there are more than 80 different autoimmune diseases, which are a significant health problem in the elderly. The table below lists several of the most common autoimmune diseases, the antigens that are targeted, and the segment of the adaptive immune response that causes the damage.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Autoantigen</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease</td>
<td>Tissue transglutaminase</td>
<td>Damage to small intestine</td>
</tr>
<tr>
<td>Diabetes mellitus type I</td>
<td>Beta cells of pancreas</td>
<td>Low insulin production; inability to regulate serum glucose</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>Thyroid-stimulating hormone receptor (antibody blocks receptor)</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>Thyroid-stimulating hormone receptor (antibody mimics hormone and stimulates receptor)</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td>Nuclear DNA and proteins</td>
<td>Damage of many body systems</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor in neuromuscular junctions</td>
<td>Debilitating muscle weakness</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Joint capsule antigens</td>
<td>Chronic inflammation of joints</td>
</tr>
</tbody>
</table>

Chapter Review

The immune response can be under-reactive or over-reactive. Suppressed immunity can result from inherited genetic defects or by acquiring viruses. Over-reactive immune responses include the hypersensitivities: B cell- and T cell-mediated immune responses designed to control pathogens, but that lead to symptoms or medical complications. The worst cases of over-reactive immune responses are autoimmune diseases, where an individual’s immune system attacks his or her own body because of the breakdown of immunological tolerance. These diseases are more common in the aged, so treating them will be a challenge in the future as the aged population in the world increases.

Critical Thinking Questions

Describe anaphylactic shock in someone sensitive to peanuts?
Describe rheumatic fever and how tolerance is broken.
Learning Objectives

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

- Explain why blood typing is important and what happens when mismatched blood is used in a transfusion
- Describe how tissue typing is done during organ transplantation and the role of transplant anti-rejection drugs
- Show how the immune response is able to control some cancers and how this immune response might be enhanced by cancer vaccines

The immune responses to transplanted organs and to cancer cells are both important medical issues. With the use of tissue typing and anti-rejection drugs, transplantation of organs and the control of the anti-transplant immune response have made huge strides in the past 50 years. Today, these procedures are commonplace. Tissue typing is the determination of MHC molecules in the tissue to be transplanted to better match the donor to the recipient. The immune response to cancer, on the other hand, has been more difficult to understand and control. Although it is clear that the immune system can recognize some cancers and control them, others seem to be resistant to immune mechanisms.
Tissue Transplantation

Tissue transplantation is more complicated than blood transfusions because of two characteristics of MHC molecules. These molecules are the major cause of transplant rejection (hence the name “histocompatibility”). **MHC polygeny** refers to the multiple MHC proteins on cells, and **MHC polymorphism** refers to the multiple alleles for each individual MHC locus. Thus, there are many alleles in the human population that can be expressed. When a donor organ expresses MHC molecules that are different from the recipient, the latter will often mount a cytotoxic T cell response to the organ and reject it. Histologically, if a biopsy of a transplanted organ exhibits massive infiltration of T lymphocytes within the first weeks after transplant, it is a sign that the transplant is likely to fail. The response is a classical, and very specific, primary T cell immune response. As far as medicine is concerned, the immune response in this scenario does the patient no good at all and causes significant harm.

<table>
<thead>
<tr>
<th>Gene</th>
<th># of alleles</th>
<th># of possible MHC I protein components</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2132</td>
<td>1527</td>
</tr>
<tr>
<td>B</td>
<td>2798</td>
<td>2110</td>
</tr>
<tr>
<td>C</td>
<td>1672</td>
<td>1200</td>
</tr>
<tr>
<td>E</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>F</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>G</td>
<td>50</td>
<td>16</td>
</tr>
</tbody>
</table>
Table 2. Partial Table of Alleles of the Human MHC (Class II)

<table>
<thead>
<tr>
<th>Gene</th>
<th># of alleles</th>
<th># of possible MHC II protein components</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRA</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>DRB</td>
<td>1297</td>
<td>958</td>
</tr>
<tr>
<td>DQA1</td>
<td>49</td>
<td>31</td>
</tr>
<tr>
<td>DQB1</td>
<td>179</td>
<td>128</td>
</tr>
<tr>
<td>DPA1</td>
<td>36</td>
<td>18</td>
</tr>
<tr>
<td>DPB1</td>
<td>158</td>
<td>136</td>
</tr>
<tr>
<td>DMA</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>DMB</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>DOA</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>DOB</td>
<td>13</td>
<td>5</td>
</tr>
</tbody>
</table>

Immunosuppressive drugs such as cyclosporine A have made transplants more successful, but matching the MHC molecules is still key. In humans, there are six MHC molecules that show the most polymorphisms, three class I molecules (A, B, and C) and three class II molecules called DP, DQ, and DR. A successful transplant usually requires a match between at least 3–4 of these molecules, with more matches associated with greater success. Family members, since they share a similar genetic background, are much more likely to share MHC molecules than unrelated individuals do. In fact, due to the extensive polymorphisms in these MHC molecules, unrelated donors are found only through a worldwide database. The system is not foolproof however, as there are not enough individuals in the system to provide the organs necessary to treat all patients needing them.

One disease of transplantation occurs with bone marrow transplants, which are used to treat various diseases, including SCID and leukemia. Because the bone marrow cells being transplanted contain lymphocytes capable of mounting an immune response, and because the recipient’s immune response has been destroyed before receiving the transplant, the donor cells may attack the recipient tissues, causing -raft-versus-host disease. Symptoms of this disease, which usually include a rash and damage to the liver and mucosa, are variable, and attempts have been made to moderate the disease by first removing mature T cells from the donor bone marrow before transplanting it.
Immune Responses Against Cancer

It is clear that with some cancers, for example Kaposi’s sarcoma, a healthy immune system does a good job at controlling them. This disease, which is caused by the human herpesvirus, is almost never observed in individuals with strong immune systems, such as the young and immunocompetent. Other examples of cancers caused by viruses include liver cancer caused by the hepatitis B virus and cervical cancer caused by the human papilloma virus. As these last two viruses have vaccines available for them, getting vaccinated can help prevent these two types of cancer by stimulating the immune response.

On the other hand, as cancer cells are often able to divide and mutate rapidly, they may escape the immune response, just as certain pathogens such as HIV do. There are three stages in the immune response to many cancers: elimination, equilibrium, and escape. Elimination occurs when the immune response first develops toward tumor-specific antigens specific to the cancer and actively kills most cancer cells, followed by a period of controlled equilibrium during which the remaining cancer cells are held in check. Unfortunately, many cancers mutate, so they no longer express any specific antigens for the immune system to respond to, and a subpopulation of cancer cells escapes the immune response, continuing the disease process.

This fact has led to extensive research in trying to develop ways to enhance the early immune response to completely eliminate the early cancer and thus prevent a later escape. One method that has shown some success is the use of cancer vaccines, which differ from viral and bacterial vaccines in that they are directed against the cells of one’s own body. Treated cancer cells are injected into cancer patients to enhance their anti-cancer immune response and thereby prolong survival. The immune system has the capability to detect these cancer cells and proliferate faster than the cancer cells do, overwhelming the cancer in a similar way as they do for viruses. Cancer vaccines have been developed for malignant melanoma, a highly fatal skin cancer, and renal (kidney) cell carcinoma. These vaccines are still in the development stages, but some positive and encouraging results have been obtained clinically.

It is tempting to focus on the complexity of the immune system and the problems it causes as a negative. The upside to immunity, however, is so much greater: The benefit of staying alive far outweighs the negatives caused when the system does sometimes go awry. Working on “autopilot,” the immune system helps to maintain your health and kill pathogens. The only time you really miss the immune response is when it is not being effective and illness results, or, as in the extreme case of HIV disease, the immune system is gone completely.
Everyday Connection: How Stress Affects the Immune Response

The Connections between the Immune, Nervous, and Endocrine Systems of the Body

The immune system cannot exist in isolation. After all, it has to protect the entire body from infection. Therefore, the immune system is required to interact with other organ systems, sometimes in complex ways. Thirty years of research focusing on the connections between the immune system, the central nervous system, and the endocrine system have led to a new science with the unwieldy name of called psychoneuroimmunology. The physical connections between these systems have been known for centuries: All primary and secondary organs are connected to sympathetic nerves. What is more complex, though, is the interaction of neurotransmitters, hormones, cytokines, and other soluble signaling molecules, and the mechanism of “crosstalk” between the systems. For example, white blood cells, including lymphocytes and phagocytes, have receptors for various neurotransmitters released by associated neurons. Additionally, hormones such as cortisol (naturally produced by the adrenal cortex) and prednisone (synthetic) are well known for their abilities to suppress T cell immune mechanisms, hence, their prominent use in medicine as long-term, anti-inflammatory drugs.

One well-established interaction of the immune, nervous, and endocrine systems is the effect of stress on immune health. In the human vertebrate evolutionary past, stress was associated with the fight-or-flight response, largely mediated by the central nervous system and the adrenal medulla. This stress was necessary for survival. The physical action of fighting or running, whichever the animal decides, usually resolves the problem in one way or another. On the other hand, there are no physical actions to resolve most modern day stresses, including short-term stressors like taking examinations and long-term stressors such as being unemployed or losing a spouse. The effect of stress can be felt by nearly every organ system, and the immune system is no exception.

Table 3. Effects of Stress on Body Systems

<table>
<thead>
<tr>
<th>System</th>
<th>Stress-related illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integumentary system</td>
<td>Acne, skin rashes, irritation</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Headaches, depression, anxiety, irritability, loss of appetite, lack of motivation, reduced mental performance</td>
</tr>
<tr>
<td>Muscular and skeletal systems</td>
<td>Muscle and joint pain, neck and shoulder pain</td>
</tr>
<tr>
<td>Circulatory system</td>
<td>Increased heart rate, hypertension, increased probability of heart attacks</td>
</tr>
<tr>
<td>Digestive system</td>
<td>Indigestion, heartburn, stomach pain, nausea, diarrhea, constipation, weight gain or loss</td>
</tr>
<tr>
<td>Immune system</td>
<td>Depressed ability to fight infections</td>
</tr>
<tr>
<td>Male reproductive system</td>
<td>Lowered sperm production, impotence, reduced sexual desire</td>
</tr>
<tr>
<td>Female reproductive system</td>
<td>Irregular menstrual cycle, reduced sexual desire</td>
</tr>
</tbody>
</table>

At one time, it was assumed that all types of stress reduced all aspects of the immune response, but the last few decades of research have painted a different picture. First, most short-term stress does not impair the immune system in healthy individuals enough to lead to a greater incidence of diseases. However, older individuals and those with suppressed immune responses due to disease or immunosuppressive drugs may respond even to short-term stressors by getting sicker more often. It has been found that short-term stress diverts the body’s resources towards enhancing innate immune responses, which have the ability to act fast and would seem to help the body prepare better for possible infections associated with the trauma that may result from a fight-or-flight exchange. The diverting of resources away from the adaptive immune response, however, causes its own share of problems in fighting disease.

Chronic stress, unlike short-term stress, may inhibit immune responses even in otherwise healthy adults. The suppression of both innate and adaptive immune responses is clearly associated with increases in some
diseases, as seen when individuals lose a spouse or have other long-term stresses, such as taking care of a spouse with a fatal disease or dementia. The new science of psychoneuroimmunology, while still in its relative infancy, has great potential to make exciting advances in our understanding of how the nervous, endocrine, and immune systems have evolved together and communicate with each other.

Chapter Review

Blood transfusion and organ transplantation both require an understanding of the immune response to prevent medical complications. Blood needs to be typed so that natural antibodies against mismatched blood will not destroy it, causing more harm than good to the recipient. Transplanted organs must be matched by their MHC molecules and, with the use of immunosuppressive drugs, can be successful even if an exact tissue match cannot be made. Another aspect to the immune response is its ability to control and eradicate cancer. Although this has been shown to occur with some rare cancers and those caused by known viruses, the normal immune response to most cancers is not sufficient to control cancer growth. Thus, cancer vaccines designed to enhance these immune responses show promise for certain types of cancer.

Critical Thinking Questions

Describe how stress affects immune responses.

Show Answer

References


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Section 20: The Respiratory System
Hold your breath. Really! See how long you can hold your breath as you continue reading. . . How long can you do it? Chances are you are feeling uncomfortable already. A typical human cannot survive without breathing for more than 3 minutes, and even if you wanted to hold your breath longer, your autonomic nervous system would take control. This is because every cell in the body needs to run the oxidative stages of cellular respiration, the process by which energy is produced in the form of adenosine triphosphate (ATP). For oxidative phosphorylation to occur, oxygen is used as a reactant and carbon dioxide is released as a waste product.

You may be surprised to learn that although oxygen is a critical need for cells, it is actually the accumulation of carbon dioxide that primarily drives your need to breathe. Carbon dioxide is exhaled and oxygen is inhaled through the respiratory system, which includes muscles to move air into and out of the lungs, passageways through which air moves, and microscopic gas exchange surfaces covered by capillaries. The circulatory system transports gases from the lungs to tissues throughout the body and vice versa. A variety of diseases can affect the respiratory system, such as asthma, emphysema, chronic obstruction pulmonary disorder (COPD), and lung cancer. All of these conditions affect the gas exchange process and result in labored breathing and other difficulties.

Figure 1. The thin air at high elevations can strain the human respiratory system. (credit: "bortescristian"/flickr.com)
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.

![Image of the respiratory system]

*Figure 1. The major respiratory structures span the nasal cavity to the diaphragm.*
Anatomy

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

## Conducting Zone

The major functions of the conducting zone are to provide a route for incoming and outgoing air, remove debris and pathogens from the incoming air, and warm and humidify the incoming air. Several structures within the conducting zone perform other functions as well. The epithelium of the nasal passages, for example, is essential to sensing odors, and the bronchial epithelium that lines the lungs can metabolize some airborne carcinogens.

### The Nose and its Adjacent Structures

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

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

Underneath the thin skin of the nose are its skeletal features. While the root and bridge of the nose consist of bone, the protruding portion of the nose is composed of cartilage. As a result, when looking at a skull, the nose is missing. The nasal bone is one of a pair of bones that lies under the root and bridge of the nose. The nasal bone articulates superiorly with the frontal bone and laterally with the maxillary bones. Septal cartilage is flexible hyaline cartilage connected to the nasal bone, forming the dorsum nasi. The alar cartilage consists of the apex of the nose; it surrounds the naris.
Figure 3. Structures of Upper Respiratory Tract

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

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

The nares and anterior portion of the nasal cavities are lined with mucous membranes, containing sebaceous glands and hair follicles that serve to prevent the passage of large debris, such as dirt, through the nasal cavity.
Anatomy

An olfactory epithelium used to detect odors is found deeper in the nasal cavity.

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

![Figure 4. Respiratory epithelium is pseudostratified ciliated columnar epithelium. Seromucous glands provide lubricating mucus. LM × 680. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)](image)

Pharynx

The pharynx is a tube formed by skeletal muscle and lined by mucous membrane that is continuous with that of the nasal cavities. The pharynx is divided into three major regions: the nasopharynx, the oropharynx, and the laryngopharynx.
Figure 5. The pharynx is divided into three regions: the nasopharynx, the oropharynx, and the laryngopharynx.

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

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

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

Larynx

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

the epiglottis and the vocal cords and muscle that help move the vocal cords to produce speech.

Figure 6. The larynx extends from the laryngopharynx and the hyoid bone to the trachea.

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

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

Trachea

The trachea (windpipe) extends from the larynx toward the lungs. The trachea is formed by 16 to 20 stacked, C-shaped pieces of hyaline cartilage that are connected by dense connective tissue. The trachealis muscle and elastic connective tissue together form the fibroelastic membrane, a flexible membrane that closes the posterior surface of the trachea, connecting the C-shaped cartilages. The fibroelastic membrane allows the trachea to
Anatomy

stretch and expand slightly during inhalation and exhalation, whereas the rings of cartilage provide structural support and prevent the trachea from collapsing. In addition, the trachealis muscle can be contracted to force air through the trachea during exhalation. The trachea is lined with pseudostratified ciliated columnar epithelium, which is continuous with the larynx. The esophagus borders the trachea posteriorly.

![Trachea and Bronchi Diagram](image)

*Figure 8. (a) The tracheal tube is formed by stacked, C-shaped pieces of hyaline cartilage. (b) The layer visible in this cross-section of tracheal wall tissue between the hyaline cartilage and the lumen of the trachea is the mucosa, which is composed of pseudostratified ciliated columnar epithelium that contains goblet cells. LM × 1220. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)*

**Bronchial Tree**

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

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

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

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

An alveolar sac is a cluster of many individual alveoli that are responsible for gas exchange. An alveolus is approximately 200 mm in diameter with elastic walls that allow the alveolus to stretch during air intake, which greatly increases the surface area available for gas exchange. Alveoli are connected to their neighbors by alveolar pores, which help maintain equal air pressure throughout the alveoli and lung.
Anatomy

Figure 10. (a) The alveolus is responsible for gas exchange. (b) A micrograph shows the alveolar structures within lung tissue. LM × 178. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

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

The simple squamous epithelium formed by type I alveolar cells is attached to a thin, elastic basement membrane. This epithelium is extremely thin and borders the endothelial membrane of capillaries. Taken together, the alveoli and capillary membranes form a respiratory membrane that is approximately 0.5 mm thick. The respiratory membrane allows gases to cross by simple diffusion, allowing oxygen to be picked up by the blood for transport and CO₂ to be released into the air of the alveoli.

Diseases of the Respiratory System: Asthma

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

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

Bronchospasms occur periodically and lead to an “asthma attack.” An attack may be triggered by environmental factors such as dust, pollen, pet hair, or dander, changes in the weather, mold, tobacco smoke, and respiratory infections, or by exercise and stress.
Symptoms of an asthma attack involve coughing, shortness of breath, wheezing, and tightness of the chest. Symptoms of a severe asthma attack that requires immediate medical attention would include difficulty breathing that results in blue (cyanotic) lips or face, confusion, drowsiness, a rapid pulse, sweating, and severe anxiety. The severity of the condition, frequency of attacks, and identified triggers influence the type of medication that an individual may require. Longer-term treatments are used for those with more severe asthma. Short-term, fast-acting drugs that are used to treat an asthma attack are typically administered via an inhaler. For young children or individuals who have difficulty using an inhaler, asthma medications can be administered via a nebulizer.

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

**Practice Question**

Watch this video to learn more about what happens during an asthma attack. What are the three changes that occur inside the airways during an asthma attack?
Chapter Review

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

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

Critical Thinking Questions

Describe the three regions of the pharynx and their functions.  
If a person sustains an injury to the epiglottis, what would be the physiological result?  
Compare and contrast the conducting and respiratory zones.

References


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The Lungs

Learning Objectives

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

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

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

Gross Anatomy of the Lungs

The lungs are pyramid-shaped, paired organs that are connected to the trachea by the right and left bronchi; on the inferior surface, the lungs are bordered by the diaphragm. The diaphragm is the flat, dome-shaped muscle located at the base of the lungs and thoracic cavity. The lungs are enclosed by the pleurae, which are attached to the mediastinum. The right lung is shorter and wider than the left lung, and the left lung occupies a smaller volume than the right. The cardiac notch is an indentation on the surface of the left lung, and it allows space for the heart (Figure 1). The apex of the lung is the superior region, whereas the base is the opposite region near the diaphragm. The costal surface of the lung borders the ribs. The mediastinal surface faces the midline.
Anatomy

Figure 1. Gross Anatomy of the Lungs

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

Blood Supply and Nervous Innervation of the Lungs

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

Blood Supply

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

Nervous Innervation

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

Pleura of the Lungs

Each lung is enclosed within a cavity that is surrounded by the pleura. The pleura (plural = pleurae) is a serous membrane that surrounds the lung. The right and left pleurae, which enclose the right and left lungs, respectively, are separated by the mediastinum. The pleurae consist of two layers. The visceral pleura is the layer that is superficial to the lungs, and extends into and lines the lung fissures (Figure 2). In contrast, the parietal pleura is the outer layer that connects to the thoracic wall, the mediastinum, and the diaphragm. The visceral and parietal pleurae connect to each other at the hilum. The pleural cavity is the space between the visceral and parietal layers.

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

**Everyday Connections: The Effects of Second-Hand Tobacco Smoke**

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

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

**Chapter Review**

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

**Critical Thinking Questions**

- Compare and contrast the right and left lungs.
- Why are the pleurae not damaged during normal breathing?

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Embryonic Development of the Respiratory System

Learning Objectives

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

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

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

Time Line

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

Weeks 4–7

Respiratory development in the embryo begins around week 4. Ectodermal tissue from the anterior head region invaginates posteriorly to form olfactory pits, which fuse with endodermal tissue of the developing pharynx. An olfactory pit is one of a pair of structures that will enlarge to become the nasal cavity. At about this same time, the lung bud forms. The lung bud is a dome-shaped structure composed of tissue that bulges from the foregut. The foregut is endoderm just inferior to the pharyngeal pouches. The laryngotracheal bud is a structure that forms from the longitudinal extension of the lung bud as development progresses. The portion of this structure nearest the pharynx becomes the trachea, whereas the distal end becomes more bulbous, forming bronchial buds. A bronchial bud is one of a pair of structures that will eventually become the bronchi and all other lower respiratory structures (Figure 1).
Weeks 7–16

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

Weeks 16–24

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

Weeks 24–Term

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

Fetal “Breathing”

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

Birth

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

Disorders of the Respiratory System: Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) primarily occurs in infants born prematurely. Up to 50 percent of infants born between 26 and 28 weeks and fewer than 30 percent of infants born between 30 and 31 weeks develop RDS. RDS results from insufficient production of pulmonary surfactant, thereby preventing the lungs from properly inflating at birth. A small amount of pulmonary surfactant is produced beginning at around 20 weeks; however, this is not sufficient for inflation of the lungs. As a result, dyspnea occurs and gas exchange cannot be performed properly. Blood oxygen levels are low, whereas blood carbon dioxide levels and pH are high. The primary cause of RDS is premature birth, which may be due to a variety of known or unknown causes. Other risk factors include gestational diabetes, cesarean delivery, second-born twins, and family history of RDS. The presence of RDS can lead to other serious disorders, such as septicemia (infection of the blood) or pulmonary hemorrhage. Therefore, it is important that RDS is immediately recognized and treated to prevent death and reduce the risk of developing other disorders. Medical advances have resulted in an improved ability to treat RDS and support the infant until proper lung development can occur. At the time of delivery, treatment may include resuscitation and intubation if the infant does not breathe on his or her own. These infants would need to be placed on a ventilator to mechanically assist with the breathing process. If spontaneous breathing occurs, application of nasal continuous positive airway pressure (CPAP) may be required. In addition, pulmonary surfactant is typically administered. Death due to RDS has been reduced by 50 percent due to the introduction of pulmonary surfactant therapy. Other therapies may include corticosteroids, supplemental oxygen, and assisted ventilation. Supportive therapies, such as temperature regulation, nutritional support, and antibiotics, may be administered to the premature infant as well.
Chapter Review

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

Critical Thinking Questions

During what timeframe does a fetus have enough mature structures to breathe on its own if born prematurely? Describe the other structures that develop during this phase. Describe fetal breathing movements and their purpose.

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Section 21: The Urinary System
Introduction to the Urinary System

Learning Objectives

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

- Describe the composition of urine
- Label structures of the urinary system
- Characterize the roles of each of the parts of the urinary system
- Illustrate the macroscopic and microscopic structures of the kidney
- Trace the flow of blood through the kidney
- Outline how blood is filtered in the kidney nephron
- Provide symptoms of kidney failure
- List some of the solutes filtered, secreted, and reabsorbed in different parts of the nephron
- Describe the role of a portal system in the kidney
- Explain how urine osmolarity is hormonally regulated
- Describe the regulation of major ions by the kidney
- Summarize the role of the kidneys in maintaining acid-base balance

The urinary system has roles you may be well aware of: cleansing the blood and ridding the body of wastes probably come to mind. However, there are additional, equally important functions played by the system. Take for example, regulation of pH, a function shared with the lungs and the buffers in the blood. Additionally, the regulation of blood pressure is a role shared with the heart and blood vessels. What about regulating the concentration of solutes in the blood? Did you know that the kidney is important in determining the concentration of red blood cells? Eighty-five percent of the erythropoietin (EPO) produced to stimulate red blood cell production is produced in the kidneys. The kidneys also perform the final synthesis step of vitamin D production, converting calcidiol to calcitriol, the active form of vitamin D.

If the kidneys fail, these functions are compromised or lost altogether, with devastating effects on homeostasis. The affected individual might experience weakness, lethargy, shortness of breath, anemia, widespread edema (swelling), metabolic acidosis, rising potassium levels, heart arrhythmias, and more. Each of these functions is vital to your well-being and survival. The urinary system, controlled by the nervous system, also stores urine until a convenient...
time for disposal and then provides the anatomical structures to transport this waste liquid to the outside of the body. Failure of nervous control or the anatomical structures leading to a loss of control of urination results in a condition called incontinence.

This chapter will help you to understand the anatomy of the urinary system and how it enables the physiologic functions critical to homeostasis. It is best to think of the kidney as a regulator of plasma makeup rather than simply a urine producer. As you read each section, ask yourself this question: “What happens if this does not work?” This question will help you to understand how the urinary system maintains homeostasis and affects all the other systems of the body and the quality of one’s life.

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Physical Characteristics of Urine

Learning Objectives

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

- Compare and contrast blood plasma, glomerular filtrate, and urine characteristics
- Describe the characteristics of a normal urine sample, including normal range of pH, osmolarity, and volume

The urinary system’s ability to filter the blood resides in about 2 to 3 million tufts of specialized capillaries—the glomeruli—distributed more or less equally between the two kidneys. Because the glomeruli filter the blood based mostly on particle size, large elements like blood cells, platelets, antibodies, and albumen are excluded. The glomerulus is the first part of the nephron, which then continues as a highly specialized tubular structure responsible for creating the final urine composition. All other solutes, such as ions, amino acids, vitamins, and wastes, are filtered to create a filtrate composition very similar to plasma. The glomeruli create about 200 liters (189 quarts) of this filtrate every day, yet you excrete less than two liters of waste you call urine.

Characteristics of the urine change, depending on influences such as water intake, exercise, environmental temperature, nutrient intake, and other factors (See Table 1). Some of the characteristics such as color and odor are rough descriptors of your state of hydration. For example, if you exercise or work outside, and sweat a great deal, your urine will turn darker and produce a slight odor, even if you drink plenty of water. Athletes are often advised to consume water until their urine is clear. This is good advice; however, it takes time for the kidneys to process body fluids and store it in the bladder. Another way of looking at this is that the quality of the urine produced is an average over the time it takes to make that urine. Producing clear urine may take only a few minutes if you are drinking a lot of water or several hours if you are working outside and not drinking much.

<table>
<thead>
<tr>
<th>Table 1. Normal Urine Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Color</td>
</tr>
<tr>
<td>Odor</td>
</tr>
<tr>
<td>Volume</td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>Specific gravity</td>
</tr>
<tr>
<td>Osmolarity</td>
</tr>
<tr>
<td>Urobilinogen</td>
</tr>
<tr>
<td>White blood cells</td>
</tr>
<tr>
<td>Leukocyte esterase</td>
</tr>
</tbody>
</table>
Table 1. Normal Urine Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>None or trace</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;0.3 mg/100 mL</td>
</tr>
<tr>
<td>Ketones</td>
<td>None</td>
</tr>
<tr>
<td>Nitrites</td>
<td>None</td>
</tr>
<tr>
<td>Blood</td>
<td>None</td>
</tr>
<tr>
<td>Glucose</td>
<td>None</td>
</tr>
</tbody>
</table>

**Urinalysis** (urine analysis) often provides clues to renal disease. Normally, only traces of protein are found in urine, and when higher amounts are found, damage to the glomeruli is the likely basis. Unusually large quantities of urine may point to diseases like diabetes mellitus or hypothalamic tumors that cause diabetes insipidus. The color of urine is determined mostly by the breakdown products of red blood cell destruction (Figure 1).

The “heme” of hemoglobin is converted by the liver into water-soluble forms that can be excreted into the bile and indirectly into the urine. This yellow pigment is **urochrome**. Urine color may also be affected by certain foods like beets, berries, and fava beans. A kidney stone or a cancer of the urinary system may produce sufficient bleeding to manifest as pink or even bright red urine. Diseases of the liver or obstructions of bile drainage from the liver impart a dark “tea” or “cola” hue to the urine. Dehydration produces darker, concentrated urine that may also possess the slight odor of ammonia. Most of the ammonia produced from protein breakdown is converted into urea by the liver, so ammonia is rarely detected in fresh urine. The strong ammonia odor you may detect in bathrooms or alleys is due to the breakdown of urea into ammonia by bacteria in the environment. About one in five people detect a distinctive odor in their urine after consuming asparagus; other foods such as onions, garlic, and fish can impart their own aromas! These food-caused odors are harmless.

Urine volume varies considerably. The normal range is one to two liters per day. The kidneys must produce a minimum urine volume of about 500 mL/day to rid the body of wastes. Output below this level may be caused by severe dehydration or renal disease and is termed **oliguria**. The virtual absence of urine production is termed **anuria**. Excessive urine production is **polyuria**, which may be due to diabetes mellitus or diabetes insipidus. In diabetes mellitus, blood glucose levels exceed the number of available sodium-glucose transporters in the kidney, and glucose appears in the urine. The osmotic nature of glucose attracts water, leading to its loss in the urine. In the case of diabetes insipidus, insufficient pituitary antidiuretic hormone (ADH) release or insufficient numbers of ADH receptors in the collecting ducts means that too few water channels are inserted into the cell membranes that line the collecting ducts of the kidney. Insufficient numbers of water channels (aquaporins) reduce water absorption, resulting in high volumes of very dilute urine.
Table 2. Urine Volumes

<table>
<thead>
<tr>
<th>Volume condition</th>
<th>Volume</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1–2 L/day</td>
<td>Diabetes mellitus; diabetes insipidus; excess caffeine or alcohol; kidney disease; certain drugs, such as diuretics; sickle cell anemia; excessive water intake</td>
</tr>
<tr>
<td>Polyuria</td>
<td>&gt;2.5 L/day</td>
<td>Dehydration; blood loss; diarrhea; cardiogenic shock; kidney disease; enlarged prostate</td>
</tr>
<tr>
<td>Oliguria</td>
<td>300–500 mL/day</td>
<td>Dehydration; blood loss; diarrhea; cardiogenic shock; kidney disease; enlarged prostate</td>
</tr>
<tr>
<td>Anuria</td>
<td>&lt;50 mL/day</td>
<td>Kidney failure; obstruction, such as kidney stone or tumor; enlarged prostate</td>
</tr>
</tbody>
</table>

The pH (hydrogen ion concentration) of the urine can vary more than 1000-fold, from a normal low of 4.5 to a maximum of 8.0. Diet can influence pH; meats lower the pH, whereas citrus fruits, vegetables, and dairy products raise the pH. Chronically high or low pH can lead to disorders, such as the development of kidney stones or osteomalacia.

Specific gravity is a measure of the quantity of solutes per unit volume of a solution and is traditionally easier to measure than osmolarity. Urine will always have a specific gravity greater than pure water (water = 1.0) due to the presence of solutes. Laboratories can now measure urine osmolarity directly, which is a more accurate indicator of urinary solutes than specific gravity. Remember that osmolarity is the number of osmoles or milliosmoles per liter of fluid (mOsmol/L). Urine osmolarity ranges from a low of 50–100 mOsmol/L to as high as 1200 mOsmol/L H₂O.

Cells are not normally found in the urine. The presence of leukocytes may indicate a urinary tract infection. Leukocyte esterase is released by leukocytes; if detected in the urine, it can be taken as indirect evidence of a urinary tract infection (UTI).

Protein does not normally leave the glomerular capillaries, so only trace amounts of protein should be found in the urine, approximately 10 mg/100 mL in a random sample. If excessive protein is detected in the urine, it usually means that the glomerulus is damaged and is allowing protein to “leak” into the filtrate.

Ketones are byproducts of fat metabolism. Finding ketones in the urine suggests that the body is using fat as an energy source in preference to glucose. In diabetes mellitus when there is not enough insulin (type I diabetes mellitus) or because of insulin resistance (type II diabetes mellitus), there is plenty of glucose, but without the action of insulin, the cells cannot take it up, so it remains in the bloodstream. Instead, the cells are forced to use fat as their energy source, and fat consumed at such a level produces excessive ketones as byproducts. These excess ketones will appear in the urine. Ketones may also appear if there is a severe deficiency of proteins or carbohydrates in the diet.

Nitrates (NO₃⁻) occur normally in the urine. Gram-negative bacteria metabolize nitrate into nitrite (NO₂⁻), and its presence in the urine is indirect evidence of infection.

There should be no blood found in the urine. It may sometimes appear in urine samples as a result of menstrual contamination, but this is not an abnormal condition. Now that you understand what the normal characteristics of urine are, the next section will introduce you to how you store and dispose of this waste product and how you make it.
Chapter Review

The kidney glomerulus filters blood mainly based on particle size to produce a filtrate lacking cells or large proteins. Most of the ions and molecules in the filtrate are needed by the body and must be reabsorbed farther down the nephron tubules, resulting in the formation of urine. Urine characteristics change depending on water intake, exercise, environmental temperature, and nutrient intake. Urinalysis analyzes characteristics of the urine and is used to diagnose diseases. A minimum of 400 to 500 mL urine must be produced daily to rid the body of wastes. Excessive quantities of urine may indicate diabetes insipidus or diabetes mellitus. The pH range of urine is 4.5 to 8.0, and is affected by diet. Osmolarity ranges from 50 to 1200 milliosmoles, and is a reflection of the amount of water being recovered or lost by renal nephrons.

Critical Thinking Questions

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

Both diabetes mellitus and diabetes insipidus produce large urine volumes, but how would other characteristics of the urine differ between the two diseases?
Gross Anatomy of Urine Transport

Learning Objectives

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

- Identify the ureters, urinary bladder, and urethra, as well as their location, structure, histology, and function
- Compare and contrast urethras of individuals with egg producing and conducting organs and those with sperm producing and conducting organs.
- Describe the micturition reflex
- Describe voluntary and involuntary neural control of micturition

Rather than start with urine formation, this section will start with urine excretion. Urine is a fluid of variable composition that requires specialized structures to remove it from the body safely and efficiently. Blood is filtered, and the filtrate is transformed into urine at a relatively constant rate throughout the day. This processed liquid is stored until a convenient time for excretion. All structures involved in the transport and storage of the urine are large enough to be visible to the naked eye. This transport and storage system not only stores the waste, but it protects the tissues from damage due to the wide range of pH and osmolarity of the urine, prevents infection by foreign organisms, and for those with sperm producing and conducting organs, provides reproductive functions.

Urethra

The **urethra** transports urine from the bladder to the outside of the body for disposal. The urethra is the only urologic organ that shows any significant anatomic difference between those with egg producing and conducting (EPC) organs and those with sperm producing and conducting (SPC) organs; all other urine transport structures are identical.

![Figure 1](image-url) 

*Figure 1. The urethra transports urine from the bladder to the outside of the body. This image shows (a) the urethra of someone with EPC organs and (b) a urethra of someone with SPC organs.*
The urethra in both those with EPC and SPC organs begins inferior and central to the two ureteral openings forming the three points of a triangular-shaped area at the base of the bladder called the **trigone** (Greek *tri-* = “triangle” and the root of the word “trigonometry”). The urethra tracks posterior and inferior to the pubic symphysis (see Figure 1). In both those with EPC and SPC organs, the proximal urethra is lined by transitional epithelium, whereas the terminal portion is a nonkeratinized, stratified squamous epithelium. In those with SPC organs, pseudostratified columnar epithelium lines the urethra between these two cell types. Voiding is regulated by an involuntary autonomic nervous system-controlled **internal urinary sphincter**, consisting of smooth muscle and voluntary skeletal muscle that forms the **external urinary sphincter** below it.

**Urethra of Individuals with EPC Organs**

The external urethral orifice is embedded in the anterior vaginal wall inferior to the clitoris, superior to the vaginal opening (introitus), and medial to the labia minora. Its short length, about 4 cm, is less of a barrier to fecal bacteria than the longer urethra of those with SPC organs, and the best explanation for the greater incidence of UTI in those with EPC organs. Voluntary control of the external urethral sphincter is a function of the pudendal nerve. It arises in the sacral region of the spinal cord, traveling via the S2–S4 nerves of the sacral plexus.

**Urethra of Individuals with SPC Organs**

The urethra of those with SPC organs passes through the prostate gland immediately inferior to the bladder before passing below the pubic symphysis (see Figure 1b). The length of the urethra in those with SPC organs varies between individuals but averages 20 cm in length. It is divided into four regions: the preprostatic urethra, the prostatic urethra, the membranous urethra, and the spongy or penile urethra. The preprostatic urethra is very short and incorporated into the bladder wall. The prostatic urethra passes through the prostate gland. During ejaculation, it receives sperm via the ejaculatory ducts and secretions from the seminal vesicles. Paired bulbourethral glands produce and secrete mucus into the urethra to buffer urethral pH during sexual stimulation. The mucus neutralizes the usually acidic environment and lubricates the urethra, decreasing the resistance to ejaculation. The membranous urethra passes through the deep muscles of the perineum, where it is invested by the overlying urethral sphincters. The spongy urethra exits at the tip (external urethral orifice) of the penis after passing through the corpus spongiosum. Mucous glands are found along much of the length of the urethra and protect the urethra from extremes of urine pH. Innervation is the same in both those with SPC and EPC organs.

**Bladder**

The urinary bladder collects urine from both ureters. The bladder lies anterior to the uterus in those with EPC organs, posterior to the pubic bone and anterior to the rectum. During late pregnancy, its capacity is reduced due to compression by the enlarging uterus, resulting in increased frequency of urination. In those with SPC organs, the anatomy is similar, minus the uterus, and with the addition of the prostate inferior to the bladder. The bladder is partially **retroperitoneal** (outside the peritoneal cavity) with its peritoneal-covered “dome” projecting into the abdomen when the bladder is distended with urine.
The bladder is a highly distensible organ comprised of irregular crisscrossing bands of smooth muscle collectively called the **detrusor muscle**. The interior surface is made of transitional cellular epithelium that is structurally suited for the large volume fluctuations of the bladder. When empty, it resembles columnar epithelia, but when stretched, it “transitions” (hence the name) to a squamous appearance. Volumes in adults can range from nearly zero to 500–600 mL.

The detrusor muscle contracts with significant force in the young. The bladder’s strength diminishes with age, but voluntary contractions of abdominal skeletal muscles can increase intra-abdominal pressure to promote more forceful bladder emptying. Such voluntary contraction is also used in forceful defecation and childbirth.

**Micturition Reflex**

Micturition is a less-often used, but proper term for urination or voiding. It results from an interplay of involuntary and voluntary actions by the internal and external urethral sphincters. When bladder volume reaches about 150 mL, an urge to void is sensed but is easily overridden. Voluntary control of urination relies on consciously preventing relaxation of the external urethral sphincter to maintain urinary continence. As the bladder fills, subsequent urges become harder to ignore. Ultimately, voluntary constraint fails with resulting **incontinence**, which will occur as bladder volume approaches 300 to 400 mL.

Normal micturition is a result of stretch receptors in the bladder wall that transmit nerve impulses to the sacral region of the spinal cord to generate a spinal reflex. The resulting parasympathetic neural outflow causes contraction of the detrusor muscle and relaxation of the involuntary internal urethral sphincter. At the same time, the spinal cord inhibits somatic motor neurons, resulting in the relaxation of the skeletal muscle of the external urethral sphincter. The micturition reflex is active in infants but with maturity, children learn to override the reflex by asserting external sphincter control, thereby delaying voiding (potty training). This reflex may be preserved even in the face of spinal cord injury that results in paraplegia or quadriplegia. However, relaxation of the external sphincter may not be possible in all cases, and therefore, periodic catheterization may be necessary for bladder emptying.

Nerves involved in the control of urination include the hypogastric, pelvic, and pudendal. Voluntary micturition requires an intact spinal cord and functional pudendal nerve arising from the **sacral micturition center**. Since
Anatomy

the external urinary sphincter is voluntary skeletal muscle, actions by cholinergic neurons maintain contraction (and thereby continence) during filling of the bladder. At the same time, sympathetic nervous activity via the hypogastric nerves suppresses contraction of the detrusor muscle. With further bladder stretch, afferent signals traveling over sacral pelvic nerves activate parasympathetic neurons. This activates efferent neurons to release acetylcholine at the neuromuscular junctions, producing detrusor contraction and bladder emptying.

Figure 3. Nerves Innervating the Urinary System

Ureters

The kidneys and ureters are completely retroperitoneal, and the bladder has a peritoneal covering only over the dome. As urine is formed, it drains into the calyces of the kidney, which merge to form the funnel-shaped renal pelvis in the hilum of each kidney. The hilum narrows to become the ureter of each kidney. As urine passes through the ureter, it does not passively drain into the bladder but rather is propelled by waves of peristalsis. As the ureters enter the pelvis, they sweep laterally, hugging the pelvic walls. As they approach the bladder, they turn medially and pierce the bladder wall obliquely. This is important because it creates an one-way valve (a **physiological sphincter** rather than an **anatomical sphincter**) that allows urine into the bladder but prevents reflux of urine from the bladder back into the ureter. Children born lacking this oblique course of the ureter through the bladder wall are susceptible to “vesicoureteral reflux,” which dramatically increases their risk of serious UTI. Pregnancy also increases the likelihood of reflux and UTI.

The ureters are approximately 30 cm long. The inner mucosa is lined with transitional epithelium (Figure 4) and scattered goblet cells that secrete protective mucus. The muscular layer of the ureter consists of longitudinal and circular smooth muscles that create the peristaltic contractions to move the urine into the bladder without the aid of gravity. Finally, a loose adventitial layer composed of collagen and fat anchors the ureters between the parietal peritoneum and the posterior abdominal wall.
Chapter Review

The urethra is the only urinary structure that differs significantly between those with EPC and SPC organs. This is due to the dual role of the urethra in those with SPC organs in transporting both urine and semen. The urethra arises from the trigone area at the base of the bladder. Urination is controlled by an involuntary internal sphincter of smooth muscle and a voluntary external sphincter of skeletal muscle. The shorter urethra of those with EPC organs contributes to a higher incidence of bladder infections. The urethra of those with SPC organs receives secretions from the prostate gland, bulbourethral gland, and seminal vesicles as well as sperm. The bladder is largely retroperitoneal and can hold up to 500–600 mL urine. Micturition is the process of voiding the urine and involves both involuntary and voluntary actions. Voluntary control of micturition requires a mature and intact sacral micturition center. It also requires an intact spinal cord. Loss of control of micturition is called incontinence and results in voiding when the bladder contains about 250 mL urine. The ureters are retroperitoneal and lead from the renal pelvis of the kidney to the trigone area at the base of the bladder. A thick muscular wall consisting of longitudinal and circular smooth muscle helps move urine toward the bladder by way of peristaltic contractions.

Critical Thinking Questions

Why are those with EPC organs more likely to contract bladder infections than those with SPC organs?
Describe how forceful urination is accomplished.
Learning Objectives

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

- Describe the external structure of the kidney, including its location, support structures, and covering
- Identify the major internal divisions and structures of the kidney
- Identify the major blood vessels associated with the kidney and trace the path of blood through the kidney
- Compare and contrast the cortical and juxtamedullary nephrons
- Name structures found in the cortex and medulla
- Describe the physiological characteristics of the cortex and medulla

The kidneys lie on either side of the spine in the retroperitoneal space between the parietal peritoneum and the posterior abdominal wall, well protected by muscle, fat, and ribs. They are roughly the size of your fist, and the male kidney is typically a bit larger than the female kidney. The kidneys are well vascularized, receiving about 25 percent of the cardiac output at rest.

External Anatomy

The left kidney is located at about the T12 to L3 vertebrae, whereas the right is lower due to slight displacement by the liver. Upper portions of the kidneys are somewhat protected by the eleventh and twelfth ribs. Each kidney weighs about 125–175 g in males and 115–155 g in females. They are about 11–14 cm in length, 6 cm wide, and 4 cm thick, and are directly covered by a fibrous capsule composed of dense, irregular connective tissue that helps to hold their shape and protect them. This capsule is covered by a shock-absorbing layer of adipose tissue called the renal fat pad, which in turn is encompassed by a tough renal fascia. The fascia and, to a lesser extent, the overlying peritoneum serve to firmly anchor the kidneys to the posterior abdominal wall in a retroperitoneal position.
Figure 1. The kidneys are slightly protected by the ribs and are surrounded by fat for protection (not shown).

On the superior aspect of each kidney is the adrenal gland. The adrenal cortex directly influences renal function through the production of the hormone aldosterone to stimulate sodium reabsorption.

Internal Anatomy

A frontal section through the kidney reveals an outer region called the renal cortex and an inner region called the medulla. The renal columns are connective tissue extensions that radiate downward from the cortex through the medulla to separate the most characteristic features of the medulla, the renal pyramids and renal papillae. The papillae are bundles of collecting ducts that transport urine made by nephrons to the calyces of the kidney for excretion. The renal columns also serve to divide the kidney into 6–8 lobes and provide a supportive framework for vessels that enter and exit the cortex. The pyramids and renal columns taken together constitute the kidney lobes.

Figure 2. Left Kidney
Renal Hilum

The renal hilum is the entry and exit site for structures servicing the kidneys: vessels, nerves, lymphatics, and ureters. The medial-facing hila are tucked into the sweeping convex outline of the cortex. Emerging from the hilum is the renal pelvis, which is formed from the major and minor calyces in the kidney. The smooth muscle in the renal pelvis funnels urine via peristalsis into the ureter. The renal arteries form directly from the descending aorta, whereas the renal veins return cleansed blood directly to the inferior vena cava. The artery, vein, and renal pelvis are arranged in an anterior-to-posterior order.

Nephrons and Vessels

The renal artery first divides into segmental arteries, followed by further branching to form interlobar arteries that pass through the renal columns to reach the cortex. The interlobar arteries, in turn, branch into arcuate arteries, cortical radiate arteries, and then into afferent arterioles. The afferent arterioles service about 1.3 million r

Nephrons are the “functional units” of the kidney; they cleanse the blood and balance the constituents of the circulation. The afferent arterioles form a tuft of high-pressure capillaries about 200 µm in diameter, the glomerulus. The rest of the nephron consists of a continuous sophisticated tubule whose proximal end surrounds the glomerulus in an intimate embrace—this is Bowman’s capsule. The glomerulus and Bowman’s capsule together form the renal corpuscle. As mentioned earlier, these glomerular capillaries filter the blood based on particle size. After passing through the renal corpuscle, the capillaries form a second arteriole, the efferent arteriole. These will next form a capillary network around the more distal portions of the nephron tubule, the peritubular capillaries and vasa recta, before returning to the venous system. As the glomerular filtrate progresses through the nephron, these capillary networks recover most of the solutes and water, and return them to the circulation. Since a capillary bed (the glomerulus) drains into a vessel that in turn forms a second capillary bed, the definition of a portal system is met. This is the only portal system in which an arteriole is found between the first and second capillary beds. (Portal systems also link the hypothalamus to the anterior pituitary, and the blood vessels of the digestive viscera to the liver.)
Cortex

In a dissected kidney, it is easy to identify the cortex; it appears lighter in color compared to the rest of the kidney. All of the renal corpuscles as well as both the proximal convoluted tubules (PCTs) and distal convoluted tubules are found here. Some nephrons have a short loop of Henle that does not dip beyond the cortex. These nephrons are called cortical nephrons. About 15 percent of nephrons have long loops of Henle that extend deep into the medulla and are called juxtamedullary nephrons.

Chapter Review

As noted previously, the structure of the kidney is divided into two principle regions—the peripheral rim of cortex and the central medulla. The two kidneys receive about 25 percent of cardiac output. They are protected in the retroperitoneal space by the renal fat pad and overlying ribs and muscle. Ureters, blood vessels, lymph vessels, and nerves enter and leave at the renal hilum. The renal arteries arise directly from the aorta, and the renal veins drain directly into the inferior vena cava. Kidney function is derived from the actions of about 1.3 million nephrons per kidney; these are the “functional units.” A capillary bed, the glomerulus, filters blood and the filtrate is captured by Bowman’s capsule. A portal system is formed when the blood flows through a second capillary bed.
surrounding the proximal and distal convoluted tubules and the loop of Henle. Most water and solutes are recovered by this second capillary bed. This filtrate is processed and finally gathered by collecting ducts that drain into the minor calyces, which merge to form major calyces; the filtrate then proceeds to the renal pelvis and finally the ureters.

Critical Thinking Questions

What anatomical structures provide protection to the kidney?
How does the renal portal system differ from the hypothalamo–hypophyseal and digestive portal systems?
Name the structures found in the renal hilum.

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Microscopic Anatomy of the Kidney

Learning Objectives

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

- Distinguish the histological differences between the renal cortex and medulla
- Describe the structure of the filtration membrane
- Identify the major structures and subdivisions of the renal corpuscles, renal tubules, and renal capillaries
- Discuss the function of the peritubular capillaries and vasa recta
- Identify the location of the juxtaglomerular apparatus and describe the cells that line it
- Describe the histology of the proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting ducts

The renal structures that conduct the essential work of the kidney cannot be seen by the naked eye. Only a light or electron microscope can reveal these structures. Even then, serial sections and computer reconstruction are necessary to give us a comprehensive view of the functional anatomy of the nephron and its associated blood vessels.

Nephrons: The Functional Unit

Nephrons take a simple filtrate of the blood and modify it into urine. Many changes take place in the different parts of the nephron before urine is created for disposal. The term forming urine will be used hereafter to describe the filtrate as it is modified into true urine. The principle task of the nephron population is to balance the plasma to homeostatic set points and excrete potential toxins in the urine. They do this by accomplishing three principle functions—filtration, reabsorption, and secretion. They also have additional secondary functions that exert control in three areas: blood pressure (via production of renin), red blood cell production (via the hormone EPO), and calcium absorption (via conversion of calcidiol into calcitriol, the active form of vitamin D).

Renal Corpuscle

As discussed earlier, the renal corpuscle consists of a tuft of capillaries called the glomerulus that is largely surrounded by Bowman’s (glomerular) capsule. The glomerulus is a high-pressure capillary bed between afferent and efferent arterioles. Bowman’s capsule surrounds the glomerulus to form a lumen, and captures and directs this filtrate to the PCT. The outermost part of Bowman’s capsule, the parietal layer, is a simple squamous epithelium. It transitions onto the glomerular capillaries in an intimate embrace to form the visceral layer of the capsule. Here, the cells are not squamous, but uniquely shaped cells (podocytes) extending finger-like arms (pedicels) to cover the glomerular capillaries (Figure 1).
Figure 1. Podocytes interdigitate with structures called pedicels and filter substances in a way similar to fenestrations. In (a), the large cell body can be seen at the top right corner, with branches extending from the cell body. The smallest finger-like extensions are the pedicels. Pedicels on one podocyte always interdigitate with the pedicels of another podocyte. (b) This capillary has three podocytes wrapped around it.

These projections interdigitate to form filtration slits, leaving small gaps between the digits to form a sieve. As blood passes through the glomerulus, 10 to 20 percent of the plasma filters between these sieve-like fingers to be captured by Bowman’s capsule and funneled to the PCT. Where the fenestrae (windows) in the glomerular capillaries match the spaces between the podocyte “fingers,” the only thing separating the capillary lumen and the lumen of Bowman’s capsule is their shared basement membrane (Figure 2). These three features comprise what is known as the filtration membrane. This membrane permits very rapid movement of filtrate from capillary to capsule though pores that are only 70 nm in diameter.

The fenestrations prevent filtration of blood cells or large proteins, but allow most other constituents through. These substances cross readily if they are less than 4 nm in size and most pass freely up to 8 nm in size. An additional factor affecting the ability of substances to cross this barrier is their electric charge. The proteins associated with these pores are negatively charged, so they tend to repel negatively charged substances and allow positively charged substances to pass more readily. The basement membrane prevents filtration of medium-to-large proteins such as globulins. There are also mesangial cells in the filtration membrane that can contract to help regulate the rate of filtration of the glomerulus. Overall, filtration is regulated by fenestrations in capillary endothelial cells, podocytes with filtration slits, membrane charge, and the basement membrane between capillary cells. The result is the creation of a filtrate that does not contain cells or large proteins, and has a slight predominance of positively charged substances.

Lying just outside Bowman’s capsule and the glomerulus is the juxtaglomerular apparatus (JGA) (Figure 3). At the juncture where the afferent and efferent arterioles enter and leave Bowman’s capsule, the initial part of the distal convoluted tubule (DCT) comes into direct contact
with the arterioles. The wall of the DCT at that point forms a part of the JGA known as the **macula densa**. This cluster of cuboidal epithelial cells monitors the fluid composition of fluid flowing through the DCT. In response to the concentration of Na\(^+\) in the fluid flowing past them, these cells release paracrine signals. They also have a single, nonmotile cilium that responds to the rate of fluid movement in the tubule. The paracrine signals released in response to changes in flow rate and Na\(^+\) concentration are adenosine triphosphate (ATP) and adenosine.

![Diagram of kidney structure](image)

**Figure 3.** (a) The JGA allows specialized cells to monitor the composition of the fluid in the DCT and adjust the glomerular filtration rate. (b) This micrograph shows the glomerulus and surrounding structures. LM × 1540. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

A second cell type in this apparatus is the **juxtaglomerular cell**. This is a modified, smooth muscle cell lining the afferent arteriole that can contract or relax in response to ATP or adenosine released by the macula densa. Such contraction and relaxation regulate blood flow to the glomerulus. If the osmolarity of the filtrate is too high (hyperosmotic), the juxtaglomerular cells will contract, decreasing the glomerular filtration rate (GFR) so less plasma is filtered, leading to less urine formation and greater retention of fluid. This will ultimately decrease blood osmolarity toward the physiologic norm. If the osmolarity of the filtrate is too low, the juxtaglomerular cells will relax, increasing the GFR and enhancing the loss of water to the urine, causing blood osmolarity to rise. In other words, when osmolarity goes up, filtration and urine formation decrease and water is retained. When osmolarity goes down, filtration and urine formation increase and water is lost by way of the urine. The net result of these opposing actions is to keep the rate of filtration relatively constant. A second function of the macula densa cells is to regulate renin release from the juxtaglomerular cells of the afferent arteriole (Figure 4). Active renin is a protein comprised of 304 amino acids that cleaves several amino acids from **angiotensinogen** to produce **angiotensin I**. Angiotensin I is not biologically active until converted to angiotensin II by **angiotensin-converting enzyme (ACE)** from the lungs. **Angiotensin II** is a systemic vasoconstrictor that helps to regulate blood pressure by increasing it. Angiotensin II also stimulates the release of the steroid hormone aldosterone from the adrenal cortex. Aldosterone stimulates Na\(^+\) reabsorption by the kidney, which also results in water retention and increased blood pressure.
Figure 4. The enzyme renin converts the pro-enzyme angiotensin I; the lung-derived enzyme ACE converts angiotensin I into active angiotensin II.

Proximal Convoluted Tubule (PCT)

Filtered fluid collected by Bowman’s capsule enters into the PCT. It is called convoluted due to its tortuous path. Simple cuboidal cells form this tubule with prominent microvilli on the luminal surface, forming a brush border. These microvilli create a large surface area to maximize the absorption and secretion of solutes (Na\(^+\), Cl\(^-\), glucose, etc.), the most essential function of this portion of the nephron. These cells actively transport ions across their membranes, so they possess a high concentration of mitochondria in order to produce sufficient ATP.

Loop of Henle

The descending and ascending portions of the loop of Henle (sometimes referred to as the nephron loop) are, of course, just continuations of the same tubule. They run adjacent and parallel to each other after having made a hairpin turn at the deepest point of their descent. The descending loop of Henle consists of an initial short, thick portion and long, thin portion, whereas the ascending loop consists of an initial short, thin portion followed by a long, thick portion. The descending thick portion consists of simple cuboidal epithelium similar to that of the PCT. The descending and ascending thin portions consists of simple squamous epithelium. As you will see later, these are important differences, since different portions of the loop have different permeabilities for solutes and water. The ascending thick portion consists of simple cuboidal epithelium similar to the DCT.

Distal Convoluted Tubule (DCT)

The DCT, like the PCT, is very tortuous and formed by simple cuboidal epithelium, but it is shorter than the PCT. These cells are not as active as those in the PCT; thus, there are fewer microvilli on the apical surface. However, these cells must also pump ions against their concentration gradient, so you will find of large numbers of mitochondria, although fewer than in the PCT.
Collecting Ducts

The collecting ducts are continuous with the nephron but not technically part of it. In fact, each duct collects filtrate from several nephrons for final modification. Collecting ducts merge as they descend deeper in the medulla to form about 30 terminal ducts, which empty at a papilla. They are lined with simple squamous epithelium with receptors for ADH. When stimulated by ADH, these cells will insert aquaporin channel proteins into their membranes, which as their name suggests, allow water to pass from the duct lumen through the cells and into the interstitial spaces to be recovered by the vasa recta. This process allows for the recovery of large amounts of water from the filtrate back into the blood. In the absence of ADH, these channels are not inserted, resulting in the excretion of water in the form of dilute urine. Most, if not all, cells of the body contain aquaporin molecules, whose channels are so small that only water can pass. At least 10 types of aquaporins are known in humans, and six of those are found in the kidney. The function of all aquaporins is to allow the movement of water across the lipid-rich, hydrophobic cell membrane.

Chapter Review

The functional unit of the kidney, the nephron, consists of the renal corpuscle, PCT, loop of Henle, and DCT. Cortical nephrons have short loops of Henle, whereas juxtamedullary nephrons have long loops of Henle extending into the medulla. About 15 percent of nephrons are juxtamedullary. The glomerulus is a capillary bed that filters blood principally based on particle size. The filtrate is captured by Bowman’s capsule and directed to the PCT. A filtration membrane is formed by the fused basement membranes of the podocytes and the capillary endothelial cells that they embrace. Contractile mesangial cells further perform a role in regulating the rate at which the blood is filtered. Specialized cells in the JGA produce paracrine signals to regulate blood flow and filtration rates of the glomerulus. Other JGA cells produce the enzyme renin, which plays a central role in blood pressure regulation. The filtrate enters the PCT where absorption and secretion of several substances occur. The descending and ascending limbs of the loop of Henle consist of thick and thin segments. Absorption and secretion continue in the DCT but to a lesser extent than in the PCT. Each collecting duct collects forming urine from several nephrons and responds to the posterior pituitary hormone ADH by inserting aquaporin water channels into the cell membrane to fine tune water recovery.

Critical Thinking Questions

Which structures make up the renal corpuscle?
What are the major structures comprising the filtration membrane?
Section 22: The Digestive System
Learning Objectives

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

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

The digestive system is continually at work, yet people seldom appreciate the complex tasks it performs in a choreographed biologic symphony. Consider what happens when you eat an apple. Of course, you enjoy the apple’s taste as you chew it, but in the hours that follow, unless something goes amiss and you get a stomachache, you don’t notice that your digestive system is working. You may be taking a walk or studying or sleeping, having forgotten all about the apple, but your stomach and intestines are busy digesting it and absorbing its vitamins and other nutrients. By the time any waste material is excreted, the body has appropriated all it can use from the apple.

In short, whether you pay attention or not, the organs of the digestive system perform their specific functions, allowing you to use the food you eat to keep you going. This chapter examines the structure and functions of these organs, and explores the mechanics and chemistry of the digestive processes.

Figure 1. Eating may be one of the simple pleasures in life, but digesting even one apple requires the coordinated work of many organs. (credit: “Aimanness Photography”/Flickr)

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Overview of the Digestive System

Learning Objectives

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

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

The function of the digestive system is to break down the foods you eat, release their nutrients, and absorb those nutrients into the body. Although the small intestine is the workhorse of the system, where the majority of digestion occurs, and where most of the released nutrients are absorbed into the blood or lymph, each of the digestive system organs makes a vital contribution to this process.
Figure 1. All digestive organs play integral roles in the life-sustaining process of digestion.

As is the case with all body systems, the digestive system does not work in isolation; it functions cooperatively with the other systems of the body. Consider for example, the interrelationship between the digestive and cardiovascular systems. Arteries supply the digestive organs with oxygen and processed nutrients, and veins drain the digestive tract. These intestinal veins, constituting the hepatic portal system, are unique; they do not return blood directly to the heart. Rather, this blood is diverted to the liver where its nutrients are off-loaded for processing before blood completes its circuit back to the heart. At the same time, the digestive system provides nutrients to the heart muscle and vascular tissue to support their functioning. The interrelationship of the digestive and endocrine systems is also critical. Hormones secreted by several endocrine glands, as well as endocrine cells of the pancreas, the stomach, and the small intestine, contribute to the control of digestion and nutrient metabolism. In turn, the digestive system provides the nutrients to fuel endocrine function. Table 1 gives a quick glimpse at how these other systems contribute to the functioning of the digestive system.

<table>
<thead>
<tr>
<th>Body system</th>
<th>Benefits received by the digestive system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Blood supplies digestive organs with oxygen and processed nutrients</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Endocrine hormones help regulate secretion in digestive glands and accessory organs</td>
</tr>
<tr>
<td>Integumentary</td>
<td>Skin helps protect digestive organs and synthesizes vitamin D for calcium absorption</td>
</tr>
<tr>
<td>Body system</td>
<td>Benefits received by the digestive system</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>Mucosa-associated lymphoid tissue and other lymphatic tissue defend against entry of pathogens; lacteals absorb lipids; and lymphatic vessels transport lipids to bloodstream</td>
</tr>
<tr>
<td>Muscular</td>
<td>Skeletal muscles support and protect abdominal organs</td>
</tr>
<tr>
<td>Nervous</td>
<td>Sensory and motor neurons help regulate secretions and muscle contractions in the digestive tract</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Respiratory organs provide oxygen and remove carbon dioxide</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Bones help protect and support digestive organs</td>
</tr>
<tr>
<td>Urinary</td>
<td>Kidneys convert vitamin D into its active form, allowing calcium absorption in the small intestine</td>
</tr>
</tbody>
</table>

**Digestive System Organs**

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

**Alimentary Canal Organs**

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

**Accessory Structures**

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

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

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

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

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

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

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

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

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

### Nerve Supply

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

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

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

### Blood Supply

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

Specifically, the more anterior parts of the alimentary canal are supplied with blood by arteries branching off the aortic arch and thoracic aorta. Below this point, the alimentary canal is supplied with blood by arteries branching from the abdominal aorta. The celiac trunk services the liver, stomach, and duodenum, whereas the superior and inferior mesenteric arteries supply blood to the remaining small and large intestines.
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The veins that collect nutrient-rich blood from the small intestine (where most absorption occurs) empty into the hepatic portal system. This venous network takes the blood into the liver where the nutrients are either processed or stored for later use. Only then does the blood drained from the alimentary canal viscera circulate back to the heart. To appreciate just how demanding the digestive process is on the cardiovascular system, consider that while you are “resting and digesting,” about one-fourth of the blood pumped with each heartbeat enters arteries serving the intestines.

The Peritoneum

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

Disorders of the Digestive System: Peritonitis

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

The visceral peritoneum includes multiple large folds that envelope various abdominal organs, holding them to the dorsal surface of the body wall. Within these folds are blood vessels, lymphatic vessels, and nerves that innervate the organs with which they are in contact, supplying their adjacent organs. The five major peritoneal folds are described in Table 2. Note that during fetal development, certain digestive structures, including the first portion of the small intestine (called the duodenum), the pancreas, and portions of the large intestine (the ascending and descending colon, and the rectum) remain completely or partially posterior to the peritoneum. Thus, the location of these organs is described as retroperitoneal.

<table>
<thead>
<tr>
<th>Fold</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater omentum</td>
<td>Apron-like structure that lies superficial to the small intestine and transverse colon; a site of fat deposition in people who are overweight</td>
</tr>
<tr>
<td>Falciform ligament</td>
<td>Anchors the liver to the anterior abdominal wall and inferior border of the diaphragm</td>
</tr>
<tr>
<td>Lesser omentum</td>
<td>Suspends the stomach from the inferior border of the liver; provides a pathway for structures connecting to the liver</td>
</tr>
<tr>
<td>Mesentery</td>
<td>Vertical band of tissue anterior to the lumbar vertebrae and anchoring all of the small intestine except the initial portion (the duodenum)</td>
</tr>
<tr>
<td>Mesocolon</td>
<td>Attaches two portions of the large intestine (the transverse and sigmoid colon) to the posterior abdominal wall</td>
</tr>
</tbody>
</table>

Chapter Review

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

Critical Thinking Questions

Explain how the enteric nervous system supports the digestive system. What might occur that could result in the autonomic nervous system having a negative impact on digestion? What layer of the alimentary canal tissue is capable of helping to protect the body against disease, and through what mechanism?

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Learning Objectives

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

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

The digestive system uses mechanical and chemical activities to break food down into absorbable substances during its journey through the digestive system. Table 1 provides an overview of the basic functions of the digestive organs.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Major functions</th>
<th>Other functions</th>
</tr>
</thead>
</table>
| Mouth   | • Ingests food  
          • Chews and mixes food  
          • Begins chemical breakdown of carbohydrates  
          • Moves food into the pharynx  
          • Begins breakdown of lipids via lingual lipase | • Moistens and dissolves food, allowing you to taste it  
                                                                                       • Cleans and lubricates the teeth and oral cavity  
                                                                                       • Has some antimicrobial activity |
| Pharynx | • Propels food from the oral cavity to the esophagus | • Lubricates food and passageways |
| Esophagus | • Propels food to the stomach | • Lubricates food and passageways |
| Stomach | • Mixes and churns food with gastric juices to form chyme  
          • Begins chemical breakdown of proteins  
          • Releases food into the duodenum as chyme  
          • Absorbs some fat-soluble substances (for example, alcohol, aspirin)  
          • Possesses antimicrobial functions | • Stimulates protein-digesting enzymes  
                                                                                       • Secretes intrinsic factor required for vitamin B<sub>12</sub> absorption in small intestine |
Table 1. Functions of the Digestive Organs

<table>
<thead>
<tr>
<th>Organ</th>
<th>Major functions</th>
<th>Other functions</th>
</tr>
</thead>
</table>
| Small intestine  | • Mixes chyme with digestive juices  
• Propels food at a rate slow enough for digestion and absorption  
• Absorbs breakdown products of carbohydrates, proteins, lipids, and nucleic acids, along with vitamins, minerals, and water  
• Performs physical digestion via segmentation | • Provides optimal medium for enzymatic activity |
| Accessory organs | • Liver: produces bile salts, which emulsify lipids, aiding their digestion and absorption  
• Gallbladder: stores, concentrates, and releases bile  
• Pancreas: produces digestive enzymes and bicarbonate | • Bicarbonate-rich pancreatic juices help neutralize acidic chyme and provide optimal environment for enzymatic activity |
| Large intestine  | • Further breaks down food residues  
• Absorbs most residual water, electrolytes, and vitamins produced by enteric bacteria  
• Propels feces toward rectum  
• Eliminates feces | • Food residue is concentrated and temporarily stored prior to defecation  
• Mucus eases passage of feces through colon |

Digestive Processes

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

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

Food leaves the mouth when the tongue and pharyngeal muscles propel it into the esophagus. This act of swallowing, the last voluntary act until defecation, is an example of propulsion, which refers to the movement of food through the digestive tract. It includes both the voluntary process of swallowing and the involuntary process of peristalsis. Peristalsis consists of sequential, alternating waves of contraction and relaxation of alimentary wall smooth muscles, which act to propel food along (Figure 1). These waves also play a role in mixing food with digestive juices. Peristalsis is so powerful that foods and liquids you swallow enter your stomach even if you are standing on your head.

Digestion includes both mechanical and chemical processes.
Mechanical digestion is a purely physical process that does not change the chemical nature of the food. Instead, it makes the food smaller to increase both surface area and mobility. It includes mastication, or chewing, as well as tongue movements that help break food into smaller bits and mix food with saliva. Although there may be a tendency to think that mechanical digestion is limited to the first steps of the digestive process, it occurs after the food leaves the mouth, as well. The mechanical churning of food in the stomach serves to further break it apart and expose more of its surface area to digestive juices, creating an acidic “soup” called chyme. Segmentation, which occurs mainly in the small intestine, consists of localized contractions of circular muscle of the muscularis layer of the alimentary canal. These contractions isolate small sections of the intestine, moving their contents back and forth while continuously subdividing, breaking up, and mixing the contents. By moving food back and forth in the intestinal lumen, segmentation mixes food with digestive juices and facilitates absorption.

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

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

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

Aging and the Digestive System: From Appetite Suppression to Constipation

Age-related changes in the digestive system begin in the mouth and can affect virtually every aspect of the digestive system. Taste buds become less sensitive, so food isn’t as appetizing as it once was. A slice of pizza is a challenge, not a treat, when you have lost teeth, your gums are diseased, and your salivary glands aren’t producing enough saliva. Swallowing can be difficult, and ingested food moves slowly through the alimentary canal because of reduced strength and tone of muscular tissue. Neurosensory feedback is also dampened, slowing the transmission of messages that stimulate the release of enzymes and hormones. Pathologies that affect the digestive organs—such as hiatal hernia, gastritis, and peptic ulcer disease—can occur at greater frequencies as you age. Problems in the small intestine may include duodenal ulcers, maldigestion, and malabsorption. Problems in the large intestine include hemorrhoids, diverticular disease, and constipation. Conditions that affect the function of accessory organs—and their abilities to deliver pancreatic enzymes and bile to the small intestine—include jaundice, acute pancreatitis, cirrhosis, and gallstones.

In some cases, a single organ is in charge of a digestive process. For example, ingestion occurs only in the mouth and defecation only in the anus. However, most digestive processes involve the interaction of several organs and occur gradually as food moves through the alimentary canal (Figure 2).
Figure 2. The digestive processes are ingestion, propulsion, mechanical digestion, chemical digestion, absorption, and defecation.

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

Regulatory Mechanisms

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

Neural Controls

The walls of the alimentary canal contain a variety of sensors that help regulate digestive functions. These include mechanoreceptors, chemoreceptors, and osmoreceptors, which are capable of detecting mechanical, chemical, and osmotic stimuli, respectively. For example, these receptors can sense when the presence of food has caused the stomach to expand, whether food particles have been sufficiently broken down, how much liquid is present, and the type of nutrients in the food (lipids, carbohydrates, and/or proteins). Stimulation of these receptors provokes an appropriate reflex that furthers the process of digestion. This may entail sending a message that activates the glands that secrete digestive juices into the lumen, or it may mean the stimulation of muscles within the alimentary canal, thereby activating peristalsis and segmentation that move food along the intestinal tract.
The walls of the entire alimentary canal are embedded with nerve plexuses that interact with the central nervous system and other nerve plexuses—either within the same digestive organ or in different ones. These interactions prompt several types of reflexes. Extrinsic nerve plexuses orchestrate long reflexes, which involve the central and autonomic nervous systems and work in response to stimuli from outside the digestive system. Short reflexes, on the other hand, are orchestrated by intrinsic nerve plexuses within the alimentary canal wall. These two plexuses and their connections were introduced earlier as the enteric nervous system. Short reflexes regulate activities in one area of the digestive tract and may coordinate local peristaltic movements and stimulate digestive secretions. For example, the sight, smell, and taste of food initiate long reflexes that begin with a sensory neuron delivering a signal to the medulla oblongata. The response to the signal is to stimulate cells in the stomach to begin secreting digestive juices in preparation for incoming food. In contrast, food that distends the stomach initiates short reflexes that cause cells in the stomach wall to increase their secretion of digestive juices.

Hormonal Controls

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

Chapter Review

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

Critical Thinking Questions

Offer a theory to explain why segmentation occurs and peristalsis slows in the small intestine. It has been several hours since you last ate. Walking past a bakery, you catch a whiff of freshly baked bread. What type of reflex is triggered, and what is the result?
Anatomy

The Mouth, Pharynx, and Esophagus

Learning Objectives

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

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

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

The Mouth

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

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

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

When you are chewing, you do not find it difficult to breathe simultaneously. The next time you have food in your mouth, notice how the arched shape of the roof of your mouth allows you to handle both digestion and respiration at the same time. This arch is called the palate. The anterior region of the palate serves as a wall (or septum) between the oral and nasal cavities as well as a rigid shelf against which the tongue can push food. It is created by the maxillary and palatine bones of the skull and, given its bony structure, is known as the hard palate. If you run your tongue along the roof of your mouth, you’ll notice that the hard palate ends in the posterior oral cavity, and the tissue becomes fleshier. This part of the palate, known as the soft palate, is composed mainly of skeletal muscle. You can therefore manipulate, subconsciously, the soft palate—for instance, to yawn, swallow, or sing.
Figure 1. The mouth includes the lips, tongue, palate, gums, and teeth.

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

The Tongue

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

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

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

both swallowing and speech.

As you learned in your study of the muscular system, the extrinsic muscles of the tongue are the mylohyoid, hyoglossus, styloglossus, and genioglossus muscles. These muscles originate outside the tongue and insert into connective tissues within the tongue. The mylohyoid is responsible for raising the tongue, the hyoglossus pulls it down and back, the styloglossus pulls it up and back, and the genioglossus pulls it forward. Working in concert, these muscles perform three important digestive functions in the mouth:

- Position food for optimal chewing
- Gather food into a bolus (rounded mass)
- Position food so it can be swallowed

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

Figure 2. This superior view of the tongue shows the locations and types of lingual papillae.

The Salivary Glands

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

The Major Salivary Glands

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

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

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

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

### Homeostatic Imbalances

#### The Parotid Glands: Mumps

Infections of the nasal passages and pharynx can attack any salivary gland. The parotid glands are the usual site of infection with the virus that causes mumps (paramyxovirus). Mumps manifests by enlargement and inflammation of the parotid glands, causing a characteristic swelling between the ears and the jaw. Symptoms include fever and throat pain, which can be severe when swallowing acidic substances such as orange juice. In about one-third of men who are past puberty, mumps also causes testicular inflammation, typically affecting only one testis and rarely resulting in sterility. With the increasing use and effectiveness of mumps vaccines, the incidence of mumps has decreased dramatically. According to the U.S. Centers for Disease Control and Prevention (CDC), the number of mumps cases dropped from more than 150,000 in 1968 to fewer than 1700 in 1993 to only 11 reported cases in 2011.

#### Regulation of Salivation

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

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

The Teeth

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

Types of Teeth

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

- The eight incisors, four top and four bottom, are the sharp front teeth you use for biting into food.
- The four cuspids (or canines) flank the incisors and have a pointed edge (cusp) to tear up food. These fang-like teeth are superb for piercing tough or fleshy foods.
- Posterior to the cuspids are the eight premolars (or bicusps), which have an overall flatter shape with two rounded cusps useful for mashing foods.
- The most posterior and largest are the 12 molars, which have several pointed cusps used to crush food so it is ready for swallowing. The third members of each set of three molars, top and bottom, are commonly referred to as the wisdom teeth, because their eruption is commonly delayed until early adulthood. It is not uncommon for wisdom teeth to fail to erupt; that is, they remain impacted. In these cases, the teeth are typically removed by orthodontic surgery.
Figure 4. This figure of two human dentitions shows the arrangement of teeth in the maxilla and mandible, and the relationship between the deciduous and permanent teeth.

**Anatomy of a Tooth**

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

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

Although enamel protects the underlying dentin and pulp cavity, it is still nonetheless susceptible to mechanical and chemical erosion, or what is known as tooth decay. The most common form, dental caries (cavities) develops when colonies of bacteria feeding on sugars in the mouth release acids that cause soft tissue inflammation and degradation of the calcium crystals of the enamel. The digestive functions of the mouth are summarized in Table 1.

![Figure 5. This longitudinal section through a molar in its alveolar socket shows the relationships between enamel, dentin, and pulp.](image)

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

The pharynx (throat) is involved in both digestion and respiration. It receives food and air from the mouth, and air from the nasal cavities. When food enters the pharynx, involuntary muscle contractions close off the air passageways.

A short tube of skeletal muscle lined with a mucous membrane, the pharynx runs from the posterior oral and nasal cavities to the opening of the esophagus and larynx. It has three subdivisions. The most superior, the nasopharynx, is involved only in breathing and speech. The other two subdivisions, the oropharynx and the laryngopharynx, are used for both breathing and digestion. The oropharynx begins inferior to the nasopharynx and is continuous below with the laryngopharynx (Figure 6). The inferior border of the laryngopharynx connects to the esophagus, whereas the anterior portion connects to the larynx, allowing air to flow into the bronchial tree.

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

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

Figure 6. The pharynx runs from the nasal cavity to the esophagus and the larynx.

The Esophagus

The esophagus is a muscular tube that connects the pharynx to the stomach. It is approximately 25.4 cm (10 in) in length, located posterior to the trachea, and remains in a collapsed form when not engaged in swallowing. As you can see in Figure 7, the esophagus runs a mainly straight route through the mediastinum of the thorax. To enter the abdomen, the esophagus penetrates the diaphragm through an opening called the esophageal hiatus.
Passage of Food through the Esophagus

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

Histology of the Esophagus

The mucosa of the esophagus is made up of an epithelial lining that contains non-keratinized, stratified squamous epithelium, with a layer of basal and parabasal cells. This epithelium protects against erosion from food particles. The mucosa’s lamina propria contains mucus-secreting glands. The muscularis layer changes according to location: In the upper third of the esophagus, the muscularis is skeletal muscle. In the middle third, it is both skeletal and smooth muscle. In the lower third, it is smooth muscle. As mentioned previously, the most superficial layer of the esophagus is called the adventitia, not the serosa. In contrast to the stomach and intestines, the loose connective tissue of the adventitia is not covered by a fold of visceral peritoneum. The digestive functions of the esophagus are identified in Table 2.

<table>
<thead>
<tr>
<th>Table 2. Digestive Functions of the Esophagus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Action</strong></td>
</tr>
<tr>
<td>Upper esophageal sphincter relaxation</td>
</tr>
<tr>
<td>Peristalsis</td>
</tr>
<tr>
<td>Lower esophageal sphincter relaxation</td>
</tr>
<tr>
<td>Mucus secretion</td>
</tr>
</tbody>
</table>
Deglutition

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

![Figure 8. Deglutition includes the voluntary phase and two involuntary phases: the pharyngeal phase and the esophageal phase.](image)

### The Voluntary Phase

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

### The Pharyngeal Phase

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

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

Chapter Review

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

Critical Thinking Questions

The composition of saliva varies from gland to gland. Discuss how saliva produced by the parotid gland differs in action from saliva produced by the sublingual gland. During a hockey game, the puck hits a player in the mouth, knocking out all eight of his most anterior teeth. Which teeth did the player lose and how does this loss affect food ingestion? What prevents swallowed food from entering the airways? Explain the mechanism responsible for gastroesophageal reflux. Describe the three processes involved in the esophageal phase of deglutition.

References


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The Stomach

Learning Objectives

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

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

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

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

As you will see in the sections that follow, the stomach plays several important roles in chemical digestion, including the continued digestion of carbohydrates and the initial digestion of proteins and triglycerides. Little if any nutrient absorption occurs in the stomach, with the exception of the negligible amount of nutrients in alcohol.

Structure

There are four main regions in the stomach: the cardia, fundus, body, and pylorus. The cardia (or cardiac region) is the point where the esophagus connects to the stomach and through which food passes into the stomach. Located inferior to the diaphragm, above and to the left of the cardia, is the dome-shaped fundus. Below the fundus is the body, the main part of the stomach. The funnel-shaped pylorus connects the stomach to the duodenum. The wider end of the funnel, the pyloric antrum, connects to the body of the stomach. The narrower end is called the pyloric canal, which connects to the duodenum. The smooth muscle pyloric sphincter is located at this latter point of connection and controls stomach emptying. In the absence of food, the stomach deflates inward, and its mucosa and submucosa fall into a large fold called a ruga.
The convex lateral surface of the stomach is called the greater curvature; the concave medial border is the lesser curvature. The stomach is held in place by the lesser omentum, which extends from the liver to the lesser curvature, and the greater omentum, which runs from the greater curvature to the posterior abdominal wall.

**Histology**

The wall of the stomach is made of the same four layers as most of the rest of the alimentary canal, but with adaptations to the mucosa and muscularis for the unique functions of this organ. In addition to the typical circular and longitudinal smooth muscle layers, the muscularis has an inner oblique smooth muscle layer. As a result, in addition to moving food through the canal, the stomach can vigorously churn food, mechanically breaking it down into smaller particles.
Figure 2. The stomach wall is adapted for the functions of the stomach. In the epithelium, gastric pits lead to gastric glands that secrete gastric juice. The gastric glands (one gland is shown enlarged on the right) contain different types of cells that secrete a variety of enzymes, including hydrochloride acid, which activates the protein-digesting enzyme pepsin.

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

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

- **Parietal cells**—Located primarily in the middle region of the gastric glands are parietal cells, which are among the most highly differentiated of the body’s epithelial cells. These relatively large cells produce both hydrochloric acid (HCl) and intrinsic factor. HCl is responsible for the high acidity (pH 1.5 to 3.5) of the stomach contents and is needed to activate the protein-digesting enzyme, pepsin. The acidity also kills much of the bacteria you ingest with food and helps to denature proteins, making them more available for enzymatic digestion. Intrinsic factor is a glycoprotein necessary for the absorption of vitamin B₁₂ in the small intestine.
- **Chief cells**—Located primarily in the basal regions of gastric glands are chief cells, which secrete pepsinogen, the inactive proenzyme form of pepsin. HCl is necessary for the conversion of pepsinogen to pepsin.
- **Mucous neck cells**—Gastric glands in the upper part of the stomach contain mucous neck cells that secrete thin, acidic mucus that is much different from the mucus secreted by the goblet cells of the surface epithelium. The role of this mucus is not currently known.
- **Enteroendocrine cells**—Finally, enteroendocrine cells found in the gastric glands secrete various hormones into the interstitial fluid of the lamina propria. These include gastrin, which is released mainly by enteroendocrine G cells.

Table 1 describes the digestive functions of important hormones secreted by the stomach.
## Table 1. Hormones Secreted by the Stomach

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

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

Figure 3. Gastric secretion occurs in three phases: cephalic, gastric, and intestinal. During each phase, the secretion of gastric juice can be stimulated or inhibited.
The cephalic phase (reflex phase) of gastric secretion, which is relatively brief, takes place before food enters the stomach. The smell, taste, sight, or thought of food triggers this phase. For example, when you bring a piece of sushi to your lips, impulses from receptors in your taste buds or the nose are relayed to your brain, which returns signals that increase gastric secretion to prepare your stomach for digestion. This enhanced secretion is a conditioned reflex, meaning it occurs only if you like or want a particular food. Depression and loss of appetite can suppress the cephalic reflex.

The gastric phase of secretion lasts 3 to 4 hours, and is set in motion by local neural and hormonal mechanisms triggered by the entry of food into the stomach. For example, when your sushi reaches the stomach, it creates distention that activates the stretch receptors. This stimulates parasympathetic neurons to release acetylcholine, which then provokes increased secretion of gastric juice. Partially digested proteins, caffeine, and rising pH stimulate the release of gastrin from enteroendocrine G cells, which in turn induces parietal cells to increase their production of HCl, which is needed to create an acidic environment for the conversion of pepsinogen to pepsin, and protein digestion. Additionally, the release of gastrin activates vigorous smooth muscle contractions. However, it should be noted that the stomach does have a natural means of avoiding excessive acid secretion and potential heartburn. Whenever pH levels drop too low, cells in the stomach react by suspending HCl secretion and increasing mucous secretions.

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

The Mucosal Barrier

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

Homeostatic Imbalances: Ulcers

When the Mucosal Barrier Breaks Down

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

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

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

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

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

Mechanical Digestion

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

The pylorus, which holds around 30 mL (1 fluid ounce) of chyme, acts as a filter, permitting only liquids and small food particles to pass through the mostly, but not fully, closed pyloric sphincter. In a process called gastric emptying, rhythmic mixing waves force about 3 mL of chyme at a time through the pyloric sphincter and into the duodenum. Release of a greater amount of chyme at one time would overwhelm the capacity of the small intestine to handle it. The rest of the chyme is pushed back into the body of the stomach, where it continues mixing. This process is repeated when the next mixing waves force more chyme into the duodenum.

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

Chemical Digestion

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

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

Its numerous digestive functions notwithstanding, there is only one stomach function necessary to life: the production of intrinsic factor. The intestinal absorption of vitamin B₁₂, which is necessary for both the production of mature red blood cells and normal neurological functioning, cannot occur without intrinsic factor. People who undergo total gastrectomy (stomach removal)—for life-threatening stomach cancer, for example—can survive with minimal digestive dysfunction if they receive vitamin B₁₂ injections.

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

Chapter Review

The stomach participates in all digestive activities except ingestion and defecation. It vigorously churns food. It secretes gastric juices that break down food and absorbs certain drugs, including aspirin and some alcohol. The stomach begins the digestion of protein and continues the digestion of carbohydrates and fats. It stores food as an
Anatomy

acidic liquid called chyme, and releases it gradually into the small intestine through the pyloric sphincter.

Critical Thinking Questions

Explain how the stomach is protected from self-digestion and why this is necessary.
Describe unique anatomical features that enable the stomach to perform digestive functions.

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The Small and Large Intestines

Learning Objectives

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

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

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

The Small Intestine

Chyme released from the stomach enters the small intestine, which is the primary digestive organ in the body. Not only is this where most digestion occurs, it is also where practically all absorption occurs. The longest part of the alimentary canal, the small intestine is about 3.05 meters (10 feet) long in a living person (but about twice as long in a cadaver due to the loss of muscle tone). Since this makes it about five times longer than the large intestine, you might wonder why it is called “small.” In fact, its name derives from its relatively smaller diameter of only about 2.54 cm (1 in), compared with 7.62 cm (3 in) for the large intestine. As we’ll see shortly, in addition to its length, the folds and projections of the lining of the small intestine work to give it an enormous surface area, which is approximately 200 m², more than 100 times the surface area of your skin. This large surface area is necessary for complex processes of digestion and absorption that occur within it.

Structure

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

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

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

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**Figure 1. The three regions of the small intestine are the duodenum, jejunum, and ileum.**

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

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

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

**Histology**

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

Figure 2. (a) The absorptive surface of the small intestine is vastly enlarged by the presence of circular folds, villi, and microvilli. (b) Micrograph of the circular folds. (c) Micrograph of the villi. (d) Electron micrograph of the microvilli. From left to right, LM x 56, LM x 508, EM x 196,000. (credit b-d: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Circular folds

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

Villi

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

Microvilli

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

Intestinal Glands

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

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

The roles of the cells in the small intestinal mucosa are detailed in Table 1.

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

Intestinal MALT

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

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

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

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

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

Chemical Digestion in the Small Intestine

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

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

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

### Disorders of the Small Intestine: Lactose Intolerance

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

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

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

The Large Intestine

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

### Structure

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

### Subdivisions

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

**Cecum**

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

Colon
The cecum blends seamlessly with the colon. Upon entering the colon, the food residue first travels up the ascending colon on the right side of the abdomen. At the inferior surface of the liver, the colon bends to form the right colic flexure (hepatic flexure) and becomes the transverse colon. The region defined as hindgut begins with the last third of the transverse colon and continues on. Food residue passing through the transverse colon travels across to the left side of the abdomen, where the colon angles sharply immediately inferior to the spleen, at the left colic flexure (splenic flexure). From there, food residue passes through the descending colon, which runs down the left side of the posterior abdominal wall. After entering the pelvis inferiorly, it becomes the s-shaped sigmoid colon, which extends medially to the midline (Figure 4). The ascending and descending colon, and the rectum (discussed next) are located in the retroperitoneum. The transverse and sigmoid colon are tethered to the posterior abdominal wall by the mesocolon.

Homeostatic Imbalances: Colorectal Cancer
Each year, approximately 140,000 Americans are diagnosed with colorectal cancer, and another 49,000 die from it, making it one of the most deadly malignancies. People with a family history of colorectal cancer are at increased risk. Smoking, excessive alcohol consumption, and a diet high in animal fat and protein also increase the risk. Despite popular opinion to the contrary, studies support the conclusion that dietary fiber and calcium do not reduce the risk of colorectal cancer.
Colorectal cancer may be signaled by constipation or diarrhea, cramping, abdominal pain, and rectal bleeding. Bleeding from the rectum may be either obvious or occult (hidden in feces). Since most colon cancers arise from benign mucosal growths called polyps, cancer prevention is focused on identifying these polyps. The colonoscopy is both diagnostic and therapeutic. Colonoscopy not only allows identification of precancerous polyps, the procedure also enables them to be removed before they become malignant. Screening for fecal occult blood tests and colonoscopy is recommended for those over 50 years of age.

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

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

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

*Figure 5. (a) The histologies of the large intestine and small intestine (not shown) are adapted for the digestive functions of each organ. (b) This micrograph shows the colon’s simple columnar epithelium and goblet cells. LM x 464. (credit b: Micrograph provided by the Regents of University of Michigan Medical School © 2012)*
Anatomy

Three features are unique to the large intestine: teniae coli, haustra, and epiploic appendages (Figure 6). The **teniae coli** are three bands of smooth muscle that make up the longitudinal muscle layer of the muscularis of the large intestine, except at its terminal end. Tonic contractions of the teniae coli bunch up the colon into a succession of pouches called **haustra** (singular = hostrum), which are responsible for the wrinkled appearance of the colon. Attached to the teniae coli are small, fat-filled sacs of visceral peritoneum called **epiploic appendages**. The purpose of these is unknown. Although the rectum and anal canal have neither teniae coli nor haustra, they do have well-developed layers of muscularis that create the strong contractions needed for defecation.

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

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

Bacterial Flora

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

Digestive Functions of the Large Intestine

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

**Mechanical Digestion**

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

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

**Chemical Digestion**

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

**Absorption, Feces Formation, and Defecation**

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

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

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

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

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

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

Critical Thinking Questions

Explain how nutrients absorbed in the small intestine pass into the general circulation.
Why is it important that chyme from the stomach is delivered to the small intestine slowly and in small amounts?
Describe three of the differences between the walls of the large and small intestines.

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

Learning Objectives

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

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

Chemical digestion in the small intestine relies on the activities of three accessory digestive organs: the liver, pancreas, and gallbladder. The digestive role of the liver is to produce bile and export it to the duodenum. The gallbladder primarily stores, concentrates, and releases bile. The pancreas produces pancreatic juice, which contains digestive enzymes and bicarbonate ions, and delivers it to the duodenum.
Figure 1. The liver, pancreas, and gallbladder are considered accessory digestive organs, but their roles in the digestive system are vital.

The Liver

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

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

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

![Diagram of the liver](figure.png)

*Figure 2. The liver receives oxygenated blood from the hepatic artery and nutrient-rich deoxygenated blood from the hepatic portal vein.*

**Histology**

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

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

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

Bile

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

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

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

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

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

The Pancreas

The soft, oblong, glandular pancreas lies transversely in the retroperitoneum behind the stomach. Its head is nestled into the “c-shaped” curvature of the duodenum with the body extending to the left about 15.2 cm (6 in) and ending as a tapering tail in the hilum of the spleen. It is a curious mix of exocrine (secreting digestive enzymes) and endocrine (releasing hormones into the blood) functions.
The exocrine part of the pancreas arises as little grape-like cell clusters, each called an acinus (plural = acini), located at the terminal ends of pancreatic ducts. These acinar cells secrete enzyme-rich pancreatic juice into tiny merging ducts that form two dominant ducts. The larger duct fuses with the common bile duct (carrying bile from the liver and gallbladder) just before entering the duodenum via a common opening (the hepatopancreatic ampulla). The smooth muscle sphincter of the hepatopancreatic ampulla controls the release of pancreatic juice and bile into the small intestine. The second and smaller pancreatic duct, the accessory duct (duct of Santorini), runs from the pancreas directly into the duodenum, approximately 1 inch above the hepatopancreatic ampulla. When present, it is a persistent remnant of pancreatic development.

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

**Pancreatic Juice**

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

The pancreas produces protein-digesting enzymes in their inactive forms. These enzymes are activated in the duodenum. If produced in an active form, they would digest the pancreas (which is exactly what occurs in the disease, pancreatitis). The intestinal brush border enzyme enteropeptidase stimulates the activation of trypsin from trypsinogen of the pancreas, which in turn changes the pancreatic enzymes procarboxypeptidase and chymotrypsinogen into their active forms, carboxypeptidase and chymotrypsin.
The enzymes that digest starch (amylase), fat (lipase), and nucleic acids (nuclease) are secreted in their active forms, since they do not attack the pancreas as do the protein-digesting enzymes.

Pancreatic Secretion

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

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

The Gallbladder

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

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

Chapter Review

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

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

Critical Thinking Questions

Why does the pancreas secrete some enzymes in their inactive forms, and where are these enzymes activated? 
Describe the location of hepatocytes in the liver and how this arrangement enhances their function.

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Section 23: The Reproductive System
Introduction to the Reproductive System

Learning Objectives

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

- Describe the anatomy of the sperm (spermatocyte) and egg (oocyte) producing and conducting organs, including their accessory structures
- Explain the role of pituitary hormones in reproductive function
- Trace the path of a spermatocyte or oocyte through the reproductive system
- Describe the process of spermatogenesis and oogenesis
- Explain the changes that occur in the ovary during the ovarian cycle, and in the uterus during the uterine cycle
- Describe the development and maturation of the sex organs and the emergence of physical characteristics that occur during puberty

The reproductive system plays an essential role in the production and transport of cells necessary to create a new, genetically unique individual. The entire process that supports the development of these cells is driven by hormones released both by reproductive organs and by the pituitary gland. Additionally, the hormones secreted by reproductive organs play an essential role in the growth and maintenance of the muscular and skeletal systems, and in the development of numerous other physical characteristics such as fat distribution, muscle mass, and vocal cord length. Hormones associated with this body system play a part in producing various behaviors, from aggression and irritability to sexual desire. Last but not least, for many the reproductive system has a social role in being a part of the relationship between individuals. So in terms of being named a “reproductive” system, the function of this body system is actually much more complex than to only produce offspring (as its name implies), especially since people possess these organs and hormones whether or not they ever reproduce! That being said, much of the content of this particular chapter is focused on the role of these cells, organs, and hormones in terms of their potential use for reproduction, but keep in mind that they continue to perform the same functions whether or not they are used to this end.

Figure 1. Following a surge of luteinizing hormone (LH), a secondary oocyte (immature egg cell) will be released into the oviduct, where it will then be available to be fertilized by a spermatocyte. Ovulation marks the end of the follicular phase of the ovarian cycle and the start of the luteal phase.

You will note that the terms “female” and “male” are not used within this chapter. This is because these terms, which refer to gender, do not necessarily represent the anatomical structures of those who identify with either, both, or neither of these genders. A person who identifies as male can have egg producing and conducting organs, a person who identifies as female can have a Y chromosome. For these reasons, the terms “male” and “female” in the realm of biology and medicine are not appropriate for describing human anatomy. Instead, the terms “egg-producing and conducting organs”, “gestational organs” and “sperm-producing and conducting organs” will be used. This vocabulary more completely and correctly describes the anatomical structures found in the human body.
Development of the Reproductive System

Learning Objectives

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

- Explain how bipotential tissues are directed to develop into sperm or egg producing and conducting organs
- Name the rudimentary duct systems in the embryo that are precursors to sperm and egg producing and conducting organs
- Describe the hormonal changes that bring about puberty, and the secondary sex characteristics associated with those hormones

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

Development of the Sexual Organs in the Embryo and Fetus

Egg producing and conducting (EPC) organs are considered the “fundamental” anatomy—that is, without much chemical prompting, all fertilized eggs would develop into these organs. To develop sperm producing and conducting (SPC) organs, an individual must be exposed to the cascade of factors initiated by a single gene on the Y chromosome. This is called the SRY (Sex-determining Region of the Y chromosome). Embryos that continue to develop EPC organs do not have a Y chromosome, and so they do not have the SRY gene.

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

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

Not all tissues in the reproductive tract are bipotential. The internal reproductive structures (for example egg conducting organs like the uterus, uterine tubes, and part of the vagina; and sperm conducting organs like the epididymis, ductus deferens, and seminal vesicles) form from one of two rudimentary duct systems in the embryo. For proper reproductive function in the adult, one set of these ducts must develop properly, and the other must degrade. In those with SPC organs, secretions from sustentacular cells trigger a degradation of the EPC organs (called the Müllarian duct). At the same time, testosterone secretion stimulates growth of the SPC organs (the Wolffian duct). Without such sustentacular cell secretion, the Müllerian duct will develop; without testosterone, the Wolffian duct will degrade. Thus, the developing offspring will be develop EPC organs.
Genes and hormones determine the development of reproductive organs. EPC and SPC organs develop from the same tissues in the embryo. View this animation to see a comparison of the development of structures of the reproductive systems in a growing fetus. Where are the testes located for most of gestational time?

Further Sexual Development Occurs at Puberty

**Puberty** is the stage of development at which individuals become sexually mature. As shown in the image below, a concerted release of hormones from the hypothalamus (GnRH), the anterior pituitary (LH and FSH), and the gonads (either testosterone or estrogen) is responsible for the maturation of the reproductive systems and the development of *secondary sex characteristics*, which are physical changes that serve auxiliary roles in reproduction.

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

As an individual approaches puberty, two changes in sensitivity occur. The first is a decrease of sensitivity in the hypothalamus and pituitary to negative feedback, meaning that it takes increasingly larger concentrations of sex steroid hormones to stop the production of LH and FSH. The second change in sensitivity is an increase in sensitivity of the gonads to the FSH and LH signals, meaning the gonads of adults are more responsive to gonadotropins than are the gonads of children. As a result of these two changes, the levels of LH and FSH slowly increase and lead to the enlargement and maturation of the gonads, which in turn leads to secretion of higher levels of sex hormones and the initiation of spermatogenesis and folliculogenesis.

In addition to age, multiple factors can affect the age of onset of puberty, including genetics, environment, and psychological stress. One of the more important influences may be nutrition; historical data demonstrate the effect of better and more consistent nutrition on the age of menarche (the beginning of menstruation or a period) in the United States, which decreased from an average age of approximately 17 years of age in 1860 to the current age of approximately 12.75 years in 1960, as it remains today. Some studies indicate a link between puberty onset and the amount of stored fat in an individual. This effect is more pronounced in those with EPC organs, but has been documented in those with SPC organs as well. Body fat, corresponding with secretion of the hormone leptin by adipose cells, appears to have a strong role in determining menarche. This may reflect to some extent the high metabolic costs of gestation and lactation. In those with EPC organs who are lean and highly active, such as gymnasts, there is often a delay in the onset of puberty.
During puberty, the release of LH and FSH from the anterior pituitary stimulates the gonads to produce sex hormones. Different sex steroid hormone concentrations also contribute to the development and function of secondary sexual characteristics. Examples of secondary sexual characteristics are listed in Table 1.

**Table 1. Development of the Secondary Sexual Characteristics**

<table>
<thead>
<tr>
<th>SPC organs</th>
<th>EPC organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased larynx size and deepening of the voice</td>
<td>Deposition of fat, predominantly in breasts and hips</td>
</tr>
<tr>
<td>Increased muscular development</td>
<td>Breast development</td>
</tr>
</tbody>
</table>
Table 1. Development of the Secondary Sexual Characteristics

<table>
<thead>
<tr>
<th>SPC organs</th>
<th>EPC organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth of facial, axillary, and pubic hair, and</td>
<td>Broadening of the pelvis and growth of axillary</td>
</tr>
<tr>
<td>increased growth of body hair</td>
<td>and pubic hair</td>
</tr>
</tbody>
</table>

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

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

Chapter Review

The reproductive systems of those with EPC and SPC organs begin to develop soon after conception. A gene on the Y chromosome called SRY is critical in stimulating a cascade of events that simultaneously stimulate testis development and repress the development of EPC organs. Testosterone produced by Interstitial cells in the embryonic testis stimulates the development of SPC organs. If testosterone is not present, EPC organs will develop.

Whereas the gonads and some other reproductive tissues are considered bipotential, the tissue that forms the internal reproductive structures stems from ducts that will develop into only SPC (Wolffian) or EPC (Müllerian) structures. The expression of hormones will cause one of these systems to continue to develop and the other to degrade.

Further development of the reproductive systems occurs at puberty. The initiation of the changes that occur in puberty is the result of a decrease in sensitivity to negative feedback in the hypothalamus and pituitary gland, and an increase in sensitivity of the gonads to FSH and LH stimulation. These changes lead to increases in either estrogen or testosterone, in adolescents with EPC and SPC organs, respectively. The increase in sex steroid hormones leads to maturation of the gonads and other reproductive organs. The initiation of spermatogenesis begins in those with SPC organs, and those with EPC organs begin ovulating and menstruating. Increases in sex steroid hormones also lead to the development of secondary sex characteristics such as breast development those with EPC organs and facial hair and larynx growth in those with SPC organs.

Self Check

Answer the question(s) below to see how well you understand the topics covered in the previous section.

Critical Thinking Questions

Identify the changes in sensitivity that occur in the hypothalamus, pituitary, and gonads as someone with EPC or SPC organs approaches puberty. Explain how these changes lead to the increases of sex steroid hormone secretions that drive many pubertal changes.
Explain how the internal EPC and SPC organs develop from two different duct systems. Explain what would occur during fetal development to an XY individual with a variation causing a nonfunctional SRY gene.

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Anatomy of the Sperm Producing and Conducting Organs

Learning Objectives

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

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

Unique for its role in human reproduction, a gamete is a specialized sex cell carrying 23 chromosomes—one half the number in body cells. Those with sperm producing and conducting (SPC) organs possess a gamete called a sperm cell (or spermatozoon), while those with egg producing and conducting (EPC) organs have a gamete known as an oocyte (or egg). At fertilization, the chromosomes in the sperm combine with the chromosomes in an oocyte. The function of SPC organs is to produce sperm and transfer them outside of the body, potentially into the egg conducting organs of another individual. The paired testes are a crucial component in this process, as they produce both sperm and androgens, the hormones that support the physiological function of SPC organs. In humans, the most important androgen for those with SPC organs is testosterone. Several accessory organs and ducts aid the process of sperm maturation and transport the sperm and other seminal components to the penis, which delivers sperm to the egg conducting organs. In this section, we examine each of these different structures, and discuss the process of sperm production and transport.
Anatomy

Figure 1. Click for a larger image. The sperm producing and conducting organs include the testes, the epididymides, the penis, and the ducts and glands that produce and carry semen. Sperm exit the scrotum through the ductus deferens, which is bundled in the spermatic cord. The seminal vesicles and prostate gland add fluids to the sperm to create semen.

Scrotum

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

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

**Figure 2.** This anterior view shows the structures of the scrotum and testes.

## Testes

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

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

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

**Sustentacular Cells**

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

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

Spermatogenesis

As just noted, spermatogenesis occurs in the seminiferous tubules that form the bulk of each testis. The process begins at puberty, after which time sperm are produced constantly throughout a person’s life. One production cycle, from spermatogonia through formed sperm, takes approximately 64 days. A new cycle starts approximately every 16 days, although this timing is not synchronous across the seminiferous tubules. Sperm counts—the total number of sperm a man produces—slowly decline after age 35, and some studies suggest that smoking can lower sperm counts irrespective of age.

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

cross-section of a seminiferous tubule from a rat, the lumen is the light-shaded area in the center of the image. The location of the primary spermatocytes is near the basement membrane, and the early spermatids are approaching the lumen (tissue source: rat). EM × 900. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

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

Structure of Formed Sperm

Sperm are smaller than most cells in the body; in fact, the volume of a sperm cell is 85,000 times less than that of the oocyte. Approximately 100 to 300 million sperm are produced each day, whereas typically only one oocyte is released via ovulation per month. As is true for most cells in the body, the structure of sperm cells speaks to their function. Sperm have a distinctive head, mid-piece, and tail region. The head of the sperm contains the extremely compact haploid nucleus with very little cytoplasm. These qualities contribute to the overall small size of the sperm (the head is only 5 μm long). A structure called the acrosome covers most of the head of the sperm cell as a “cap” that is filled with lysosomal enzymes important for preparing sperm to participate in fertilization. Tightly packed mitochondria fill the mid-piece of the sperm. ATP produced by these mitochondria will power the flagellum, which extends from the neck and the mid-piece through the tail of the sperm, enabling it to move the entire sperm cell. The central strand of the flagellum, the axial filament, is formed from one centriole inside the maturing sperm cell during the final stages of spermatogenesis.

![Diagram of sperm structure](image)

**Figure 5.** Sperm cells are divided into a head, containing DNA; a mid-piece, containing mitochondria; and a tail, providing motility. The acrosome is oval and somewhat flattened.

Sperm Transport

To fertilize an egg, sperm must be moved from the seminiferous tubules in the testes, through the epididymis, and—later during ejaculation—along the length of the penis and potentially out into the egg conducting organs.
Role of the Epididymis

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

Duct System

During ejaculation, sperm exit the tail of the epididymis and are pushed by smooth muscle contraction to the ductus deferens (also called the vas deferens). The ductus deferens is a thick, muscular tube that is bundled together inside the scrotum with connective tissue, blood vessels, and nerves into a structure called the spermatic cord. Because the ductus deferens is physically accessible within the scrotum, surgical sterilization to interrupt sperm delivery can be performed by cutting and sealing a small section of the ductus (vas) deferens. This procedure is called a vasectomy, and it is an effective form of birth control. Although it may be possible to reverse a vasectomy, clinicians consider the procedure permanent.

Practice Question

Watch this video to learn about a vasectomy. As described in this video, a vasectomy is a procedure in which a small section of the ductus (vas) deferens is removed from the scrotum. This interrupts the path taken by sperm through the ductus deferens. If sperm do not exit through the vas deferens, in what region of the testis do they remain?

Show Answer

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

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

Seminal Vesicles

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

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

Prostate Gland

As shown in Figure 1, the centrally located prostate gland sits anterior to the rectum at the base of the bladder surrounding the prostatic urethra (the portion of the urethra that runs within the prostate). About the size of a walnut, the prostate is formed of both muscular and glandular tissues. It excretes an alkaline, milky fluid to the passing seminal fluid—now called semen—that is critical to first coagulate (thicken) and then de-coagulate the
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semen following ejaculation. The temporary thickening of semen helps retain it within the female reproductive tract, providing time for sperm to utilize the fructose provided by seminal vesicle secretions. When the semen regains its fluid state, sperm can then pass farther into the egg conducting organs.

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

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

Bulbourethral Glands

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

Practice Question

Watch this video to explore the SPC organs and the path of sperm, which starts in the testes and ends as the sperm leave the penis through the urethra. Where are sperm deposited after they leave the ejaculatory duct?

Show Answer

The Penis

The penis is the male organ of copulation (sexual intercourse). It is flaccid for non-sexual actions, such as urination, and turgid and rod-like with sexual arousal. When erect, the stiffness of the organ allows it to penetrate into the vagina and deposit semen.
Figure 6. Three columns of erectile tissue make up most of the volume of the penis.

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

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

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

Recall that the release of NO induces relaxation of the smooth muscles that surround the penile arteries, leading to the vasodilation necessary to achieve an erection. To reverse the process of vasodilation, an enzyme called phosphodiesterase (PDE) degrades a key component of the NO signaling pathway called cGMP. There are several different forms of this enzyme, and PDE type 5 is the type of PDE found in the tissues of the penis. Scientists discovered that inhibiting PDE5 increases blood flow, and allows vasodilation of the penis to occur. PDEs and the vasodilation signaling pathway are found in the vasculature in other parts of the body. In the 1990s, clinical trials of a PDE5 inhibitor called sildenafil were initiated to treat hypertension and angina pectoris (chest pain caused by poor blood flow through the heart). The trial showed that the drug was not effective at treating heart conditions, but many people experienced erection and priapism (erection lasting longer than 4 hours). Because of this, a clinical trial was started to investigate the ability of sildenafil to promote erections in those suffering from ED. In 1998, the FDA approved the drug, marketed as Viagra®. Since approval of the drug, sildenafil and similar PDE inhibitors now generate over a billion dollars a year in sales, and are reported to be effective in treating approximately 70 to 85 percent of cases of ED. Importantly, people with health problems—especially those with cardiac disease taking nitrates—should avoid Viagra or talk to their physician to find out if they are a candidate for the use of this drug, as deaths have been reported for at-risk users.

Testosterone

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

Functions of Testosterone

The continued presence of testosterone is necessary to keep the SPC organs working properly, and Interstitial cells produce approximately 6 to 7 mg of testosterone per day. Testicular steroidogenesis (the manufacture of androgens, including testosterone) results in testosterone concentrations that are 100 times higher in the testes than in the circulation. Maintaining these normal concentrations of testosterone promotes spermatogenesis, whereas low levels of testosterone can lead to infertility. In addition to intra-testicular secretion, testosterone is also released into the systemic circulation and plays an important role in muscle development, bone growth, the development of secondary sex characteristics, and maintaining libido (sex drive). In those with EPC organs, the ovaries secrete small amounts of testosterone, although most is converted to estradiol. A small amount of testosterone is also secreted by the adrenal glands in both those with EPC and SPC organs.

Aging and SPC ORGANS

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

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

Chapter Review

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

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

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

Self Check

Answer the question(s) below to see how well you understand the topics covered in the previous section.

Critical Thinking Questions

Briefly explain why mature gametes carry only one set of chromosomes.
What special features are evident in sperm cells but not in somatic (body) cells, and how do these specializations function?
What do each of the three accessory glands of the SPC organs contribute to the semen?
Describe how penile erection occurs.
While anabolic steroids (synthetic testosterone) bulk up muscles, they can also affect testosterone production in the testis. Using what you know about negative feedback, describe what would happen to testosterone production in the testis if a someone takes large amounts of synthetic testosterone.
Anatomy of the Egg Producing and Conducting Organs and Gestational Organs

Learning Objectives

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

- Describe the structure and function of the egg producing and conducting organs
- List the steps of oogenesis
- Trace the path of an oocyte from ovary to fertilization, or to release from the body during menstruation

The egg producing and conducting (EPC) organs function to produce gametes and reproductive hormones, just like the SPC organs; however, it also has the additional task of potentially supporting a developing fetus and delivering it to the outside world. Unlike the SPC organs, the EPC organs are located primarily inside the pelvic cavity. Ovaries are the gonads, and the gamete they produce is called an oocyte (egg). We’ll discuss the production of oocytes in detail shortly. First, let’s look at some of the EPC organs.
Figure 1. The major egg producing and conducting organs are located inside the pelvic cavity.
External Genitals of those with EPC Organs

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

The superior, anterior portions of the labia minora come together to encircle the **clitoris** (or glans clitoris), an organ that originates from the same cells as the glans penis and has abundant nerves that make it important in sexual sensation and orgasm. The **hymen** is a thin membrane that sometimes partially covers the entrance to the vagina. An intact hymen cannot be used as an indication that intercourse has never occurred (“virginity”); even at birth, this is only a partial membrane, as menstrual fluid and other secretions must be able to exit the body, regardless of penile–vaginal intercourse. The vaginal opening is located between the opening of the urethra and the anus. It is flanked by outlets to the **greater vestibular glands** (or Bartholin’s glands).

**Figure 2.** The external genitalia of those with EPC organs are referred to collectively as the vulva.

Vagina

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

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

Ovaries

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

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

The Ovarian Cycle

The ovarian cycle is a set of predictable changes in the oocytes and ovarian follicles. Beginning at puberty and ending at menopause, the ovarian cycle is a roughly 28-day cycle that can be correlated with, but is not the same as, the menstrual cycle (discussed shortly). The cycle includes two interrelated processes: oogenesis (the production of gametes) and folliculogenesis (the growth and development of ovarian follicles).

Oogenesis

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

The initiation of ovulation—the release of an oocyte from the ovary—marks the transition from puberty into reproductive maturity. From then on, ovulation occurs approximately once every 28 days. Just prior to ovulation, a surge of luteinizing hormone triggers the resumption of meiosis in a primary oocyte. This initiates the transition from primary to secondary oocyte. However, as you can see in Figure 3, this cell division does not result in two identical cells. Instead, the cytoplasm is divided unequally, and one daughter cell is much larger than the other. This larger cell, the secondary oocyte, eventually leaves the ovary during ovulation. The smaller cell, called the first polar body, may or may not complete meiosis and produce second polar bodies; in either case, it eventually disintegrates. Therefore, even though oogenesis produces up to four cells, only one survives.
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Figure 3. Click for a larger image. The unequal cell division of oogenesis produces one to three polar bodies that later degrade, as well as a single haploid ovum, which is produced only if there is penetration of the secondary oocyte by a sperm cell.

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

The larger amount of cytoplasm contained in the oocyte is used to supply the developing zygote with nutrients during the period between fertilization and implantation into the uterus. Interestingly, sperm contribute only DNA at fertilization—not cytoplasm. Therefore, the cytoplasm and all of the cytoplasmic organelles in the developing embryo are of originate from the egg-producing parent. This includes mitochondria, which contain their own DNA. Scientific research in the 1980s determined that mitochondrial DNA was inherited from the ovum, meaning that you can trace your mitochondrial DNA directly to your egg-producing parent, their egg-producing parent, and so on back through your ancestors with EPC organs.

Everyday Connections: Mapping Human History with Mitochondrial DNA

When we talk about human DNA, we’re usually referring to nuclear DNA; that is, the DNA coiled into chromosomal bundles in the nucleus of our cells. We inherit half of our nuclear DNA from our sperm-producing parent, and half from our egg-producing parent. However, mitochondrial DNA (mtDNA) comes only from the mitochondria in the cytoplasm of the ovum we inherit from our egg-producing parent. That mtDNA was inherited from their egg-producing parent, who got it from their egg-producing parent, and so on. Each of our cells contains approximately 1700 mitochondria, with each mitochondrion packed with mtDNA containing approximately 37 genes.
Mutations (changes) in mtDNA occur spontaneously in a somewhat organized pattern at regular intervals in human history. By analyzing these mutational relationships, researchers have been able to determine that we can all trace our ancestry back to one person with EPC organs who lived in Africa about 200,000 years ago. Scientists have given this person the biblical name “Eve”, although they are not, of course, the first *Homo sapiens* with EPC organs. More precisely, they are our most recent common ancestor to provide mtDNA. This doesn’t mean that everyone’s mtDNA today looks exactly like that of our ancestral “Eve”. Because of the spontaneous mutations in mtDNA that have occurred over the centuries, researchers can map different “branches” off of the “main trunk” of our mtDNA family tree. Your mtDNA might have a pattern of mutations that aligns more closely with one branch, and your neighbor’s may align with another branch. Still, all branches eventually lead back to “Eve”.

But what happened to the mtDNA of all of the other *Homo sapiens* with EPC organs who were living at the time of “Eve”? Researchers explain that, over the centuries, their descendants either died childless or only with children who had SPC organs, and thus their line of mtDNA ended.

### Folliculogenesis

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

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

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

Within the growing secondary follicle, the primary oocyte now secretes a thin acellular membrane called the zona pellucida that will play a critical role in fertilization. A thick fluid, called follicular fluid, that has formed between the granulosa cells also begins to collect into one large pool, or **antrum**. Follicles in which the antrum has become large and fully formed are considered **tertiary follicles** (or antral follicles). Several follicles reach the tertiary stage at the same time, and most of these will undergo atresia. The one that does not die will continue to grow and develop until ovulation, when it will expel its secondary oocyte surrounded by several layers of granulosa cells from the ovary. Keep in mind that most follicles don’t make it to this point. In fact, roughly 99 percent of the follicles in the ovary will undergo atresia, which can occur at any stage of folliculogenesis.
Figure 4. Click for a larger image. (a) The maturation of a follicle is shown in a clockwise direction proceeding from the primordial follicles. FSH stimulates the growth of a tertiary follicle, and LH stimulates the production of estrogen by granulosa and theca cells. Once the follicle is mature, it ruptures and releases the oocyte. Cells remaining in the follicle then develop into the corpus luteum. (b) In this electron micrograph of a secondary follicle, the oocyte, theca cells (thecae folliculi), and developing antrum are clearly visible. EM × 1100. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)
The uterine tubes (also called fallopian tubes or oviducts) serve as the conduit of the oocyte from the ovary to the uterus. Each of the two uterine tubes is close to, but not directly connected to, the ovary and divided into sections. The **isthmus** is the narrow medial end of each uterine tube that is connected to the uterus. The wide distal **infundibulum** flares out with slender, finger-like projections called **fimbriae**. The middle region of the tube, called the **ampulla**, is where fertilization often occurs. The uterine tubes also have three layers: an outer serosa, a middle smooth muscle layer, and an inner mucosal layer. In addition to its mucus-secreting cells, the inner mucosa contains ciliated cells that beat in the direction of the uterus, producing a current that will be critical to move the oocyte.

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

**Practice Question**

Visit the online OER to watch a video to observe ovulation and its initiation in response to the release of FSH and LH from the pituitary gland. What specialized structures help guide the oocyte from the ovary into the uterine tube?

If the oocyte is successfully fertilized, the resulting zygote will begin to divide into two cells, then four, and so on, as it makes its way through the uterine tube and into the uterus. There, it will implant and continue to grow. If the egg is not fertilized, it will simply degrade—either in the uterine tube or in the uterus, where it may be shed with the next menstrual period.
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Figure 6. This anterior view shows the relationship of the ovaries, uterine tubes (oviducts), and uterus. Sperm enter through the vagina, and fertilization of an ovulated oocyte usually occurs in the distal uterine tube. From left to right, LM × 400, LM × 20. (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

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

Practice Question
Visit the online OER to watch a series of videos to look at the movement of the oocyte through the ovary. The cilia in the uterine tube promote movement of the oocyte. What would likely occur if the cilia were paralyzed at the time of ovulation?

The Uterus and Cervix

The uterus is the muscular organ that nourishes and supports the growing embryo. Its average size is approximately 5 cm wide by 7 cm long (approximately 2 in by 3 in), but it increases greatly in size during pregnancy. It has three sections. The portion of the uterus superior to the opening of the uterine tubes is called the fundus. The middle section of the uterus is called the body of uterus (or corpus). The cervix is the narrow inferior portion of the uterus that projects into the vagina. The cervix produces mucus secretions that become thin and stringy under the influence of high systemic plasma estrogen concentrations, and these secretions can facilitate sperm movement through the reproductive tract.

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

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

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

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

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**Disorders of EPC Organs**

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

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

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

Risk factors for cervical cancer include having unprotected sex; having multiple sexual partners; a first sexual experience at a younger age, when the cells of the cervix are not fully mature; failure to receive the HPV vaccine; a compromised immune system; and smoking. The risk of developing cervical cancer is doubled with cigarette smoking.
Figure 8. In most cases, cells infected with the HPV virus heal on their own. In some cases, however, the virus continues to spread and becomes an invasive cancer.

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

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

In 2006, the first vaccine against the high-risk types of HPV was approved. There are now two HPV vaccines available: Gardasil® and Cervarix®. Whereas these vaccines were initially only targeted for those with EPC organs, because HPV is sexually transmitted, both those with EPC and SPC organs require vaccination for this approach to achieve its maximum efficacy. A recent study suggests that the HPV vaccine has cut the rates of HPV infection by the four targeted strains at least in half. Unfortunately, the high cost of manufacturing the vaccine is currently limiting access to many people worldwide.

The Breasts

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

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

Figure 9. During lactation, milk moves from the alveoli through the lactiferous ducts to the nipple.

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

Aging and the EPC organs

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

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

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

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

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

Chapter Review

The external genitalia of those with EPC organs are collectively called the vulva. The vagina is the pathway into and out of the uterus. The penis is inserted into the vagina to deliver sperm, and the baby exits the uterus through the vagina during childbirth.

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

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

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

Self Check

Answer the question(s) below to see how well you understand the topics covered in the previous section.

Critical Thinking Questions

Follow the path of ejaculated sperm from the vagina to the oocyte. Include all structures of the EPC organs that the sperm must swim through to reach the egg.

Identify some differences between meiosis in those with SPC or EPC organs.

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

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

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Section 24: Development and Pregnancy
Learning Objectives

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

- List and explain the steps involved in fertilization
- Describe the major events in embryonic development
- Describe the major events in fetal development
- Discuss the adaptations of the body to pregnancy
- Describe the physiologic adjustments that the newborn must make in the first hours of extrauterine life
- Summarize the physiology of lactation

In approximately nine months, a single cell—a zygote—develops into a fully formed infant consisting of trillions of cells with myriad specialized functions. The dramatic changes of fertilization, embryonic development, and fetal development are followed by remarkable adaptations of the newborn to life outside the womb.

An offspring’s normal development depends upon the appropriate synthesis of structural and functional proteins. This, in turn, is governed by the genetic material inherited from the parental egg and sperm, as well as environmental factors.

Figure 1. A single fertilized egg develops over the span of nine months into an infant consisting of trillions of cells and capable of surviving outside the womb. (credit: “Seattleye”/flickr.com)

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Fertilization

Learning Objectives

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

- Describe the path taken by sperm to reach an oocyte
- Explain capacitation and its importance in fertilization
- Summarize the events that occur as a sperm fertilizes an oocyte

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

Transit of Sperm

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

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

Contact Between Sperm and Oocyte

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

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

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

![Figure 1. Before fertilization, hundreds of capacitated sperm must break through the surrounding corona radiata and zona pellucida so that one can contact and fuse with the oocyte plasma membrane.](image)

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

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

The Zygote

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

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

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

**Everyday Connections: In Vitro Fertilization**

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

A typical IVF procedure begins with egg collection. A normal ovulation cycle produces only one oocyte, but the number can be boosted significantly (to 10–20 oocytes) by administering a short course of gonadotropins. The course begins with follicle-stimulating hormone (FSH) analogs, which support the development of multiple follicles, and ends with a luteinizing hormone (LH) analog that triggers ovulation. Right before the ova would be released from the ovary, they are harvested using ultrasound-guided oocyte retrieval. In this procedure, ultrasound allows a physician to visualize mature follicles. The ova are aspirated (sucked out) using a syringe. In parallel, sperm are obtained from the person with SPC organs, or from a sperm bank. The sperm are prepared by washing to remove seminal fluid because seminal fluid contains a peptide, FPP (or, fertilization promoting peptide), that—in high concentrations—prevents capacitation of the sperm. The sperm sample is also concentrated, to increase the sperm count per milliliter.

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

The embryos are then incubated until they either reach the eight-cell stage or the blastocyst stage. In the United States, fertilized eggs are typically cultured to the blastocyst stage because this results in a higher pregnancy rate. Finally, the embryos are transferred to the uterus using a plastic catheter (tube). The diagram below illustrates the steps involved in IVF.
In vitro fertilization involves egg collection from the ovaries, fertilization in a petri dish, and the transfer of embryos into the uterus.

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

The rate of success for IVF is correlated with the age of the person with EPC organs. More than 40 percent of whose with EPC organs under 35 succeed in giving birth following IVF, but the rate drops to a little over 10 percent in those who are over 40.

Visit the website posted here in the online OER to view resources covering various aspects of fertilization, including movies and animations showing sperm structure and motility, ovulation, and fertilization.
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Hundreds of millions of sperm deposited in the vagina travel toward the oocyte, but only a few hundred actually reach it. The number of sperm that reach the oocyte is greatly reduced because of conditions within the female reproductive tract. Many sperm are overcome by the acidity of the vagina, others are blocked by mucus in the cervix, whereas others are attacked by phagocytic leukocytes in the uterus. Those sperm that do survive undergo a change in response to those conditions. They go through the process of capacitation, which improves their motility and alters the membrane surrounding the acrosome, the cap-like structure in the head of a sperm that contains the digestive enzymes needed for it to attach to and penetrate the oocyte.

The oocyte that is released by ovulation is protected by a thick outer layer of granulosa cells known as the corona radiata and by the zona pellucida, a thick glycoprotein membrane that lies just outside the oocyte’s plasma membrane. When capacitated sperm make contact with the oocyte, they release the digestive enzymes in the acrosome (the acrosomal reaction) and are thus able to attach to the oocyte and burrow through to the oocyte’s zona pellucida. One of the sperm will then break through to the oocyte’s plasma membrane and release its haploid nucleus into the oocyte. The oocyte’s membrane structure changes in response (cortical reaction), preventing any further penetration by another sperm and forming a fertilization membrane. Fertilization is complete upon unification of the haploid nuclei of the two gametes, producing a diploid zygote.

Self Check

Answer the question(s) below to see how well you understand the topics covered in the previous section.

Critical Thinking Questions

Darcy and Raul are having difficulty conceiving a child. Darcy ovulates every 28 days, and Raul’s sperm count is normal. If we could observe Raul’s sperm about an hour after ejaculation, however, we’d see that they appear to be moving only sluggishly. When Raul’s sperm eventually encounter Darcy’s oocyte, they appear to be incapable of generating an adequate acrosomal reaction. Which process has probably gone wrong?

Sherisse is a sexually active college student. On Saturday night, she has unprotected sex with her boyfriend. On Tuesday morning, she experiences the twinge of mid-cycle pain that she typically feels when she is ovulating. This makes Sherisse extremely anxious that she might soon learn she is pregnant. Is Sherisse’s concern valid? Why or why not?

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Anatomy

Embryonic Development

Learning Objectives

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

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

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

In this section, and in those that follow in this chapter, unless otherwise specified, the terms “parent” or “parental” will refer to the individual with gestational organs in whom the embryo (and later, the fetus) is developing.

Pre-Implantation Embryonic Development

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

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

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

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Figure 1. Pre-embryonic cleavages make use of the abundant cytoplasm of the conceptus as the cells rapidly divide without changing the total volume.

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

Practice Question
Visit the online OER to view a time-lapse movie of a conceptus starting at day 3. What is the first structure you see? At what point in the movie does the blastocoel first appear? What event occurs at the end of the movie?

Implantation

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

Figure 2. Click for a larger image. Ovulation, fertilization, pre-embryonic development, and implantation occur at specific locations within the female reproductive system in a time span of approximately 1 week.

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

Figure 3. Click to show larger image. During implantation, the trophoblast cells of the blastocyst adhere to the endometrium and digest endometrial cells until it is attached securely.

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

Disorders of the Development of the Embryo

In the vast majority of ectopic pregnancies, the embryo does not complete its journey to the uterus and implants in the uterine tube, referred to as a tubal pregnancy. However, there are also ovarian ectopic pregnancies (in which the egg never left the ovary) and abdominal ectopic pregnancies (in which an egg was "lost" to the abdominal cavity during the transfer from ovary to uterine tube, or in which an embryo from a
Tubal pregnancies can be caused by scar tissue within the tube following a sexually transmitted bacterial infection. The scar tissue impedes the progress of the embryo into the uterus—in some cases “snagging” the embryo and, in other cases, blocking the tube completely. Approximately one half of tubal pregnancies resolve spontaneously. Implantation in a uterine tube causes bleeding, which appears to stimulate smooth muscle contractions and expulsion of the embryo. In the remaining cases, medical or surgical intervention is necessary. If an ectopic pregnancy is detected early, the embryo’s development can be arrested by the administration of the cytotoxic drug methotrexate, which inhibits the metabolism of folic acid. If diagnosis is late and the uterine tube is already ruptured, surgical repair is essential.

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

Embryonic Membranes

During the second week of development, with the embryo implanted in the uterus, cells within the blastocyst start to organize into layers. Some grow to form the extra-embryonic membranes needed to support and protect the growing embryo: the amnion, the yolk sac, the allantois, and the chorion.
At the beginning of the second week, the cells of the inner cell mass form into a two-layered disc of embryonic cells, and a space—the amniotic cavity—opens up between it and the trophoblast (Figure 5). Cells from the upper layer of the disc (the epiblast) extend around the amniotic cavity, creating a membranous sac that forms into the amnion by the end of the second week. The amnion fills with amniotic fluid and eventually grows to surround the embryo. Early in development, amniotic fluid consists almost entirely of a filtrate of maternal plasma, but as the kidneys of the fetus begin to function at approximately the eighth week, they add urine to the volume of amniotic fluid. Floating within the amniotic fluid, the embryo—and later, the fetus—is protected from trauma and rapid temperature changes. It can move freely within the fluid and can prepare for swallowing and breathing out of the uterus.

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

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

**Embryogenesis**

As the third week of development begins, the two-layered disc of cells becomes a three-layered disc through the process of gastrulation, during which the cells transition from totipotency to multipotency. The embryo, which takes the shape of an oval-shaped disc, forms an indentation called the primitive streak along the dorsal surface of the epiblast. A node at the caudal or “tail” end of the primitive streak emits growth factors that direct cells to multiply and migrate. Cells migrate toward and through the primitive streak and then move laterally to create two new layers of cells. The first layer is the endoderm, a sheet of cells that displaces the hypoblast and lies adjacent to the yolk sac. The second layer of cells fills in as the middle layer, or mesoderm. The cells of the epiblast that remain (not having migrated through the primitive streak) become the ectoderm.
Formation of the three primary germ layers occurs during the first 2 weeks of development. The embryo at this stage is only a few millimeters in length.

Each of these germ layers will develop into specific structures in the embryo. Whereas the ectoderm and endoderm form tightly connected epithelial sheets, the mesodermal cells are less organized and exist as a loosely connected cell community. The ectoderm gives rise to cell lineages that differentiate to become the central and peripheral nervous systems, sensory organs, epidermis, hair, and nails. Mesodermal cells ultimately become the skeleton, muscles, connective tissue, heart, blood vessels, and kidneys. The endoderm goes on to form the epithelial lining of the gastrointestinal tract, liver, and pancreas, as well as the lungs (Figure 7).
Development of the Placenta

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

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

Figure 8. In the placenta, uterine and fetal blood components are conducted through the surface of the chorionic villi, but parental and fetal bloodstreams never mix directly.

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

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

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

<table>
<thead>
<tr>
<th>Table 1. Functions of the Placenta</th>
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<tr>
<td><strong>Nutrition and digestion</strong></td>
</tr>
<tr>
<td>• Mediates diffusion of maternal glucose, amino acids, fatty acids, vitamins, and minerals</td>
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<tr>
<td>• Stores nutrients during early pregnancy to accommodate increased fetal demand later in pregnancy</td>
</tr>
<tr>
<td>• Excretes and filters fetal nitrogenous wastes into parental blood</td>
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**Organogenesis**

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

Folate, one of the B vitamins, is important to the healthy development of the neural tube. A deficiency of maternal folate in the first weeks of pregnancy can result in neural tube defects, including spina bifida—a birth defect in which spinal tissue protrudes through the newborn’s vertebral column, which has failed to completely close. A more severe neural tube defect is anencephaly, a partial or complete absence of brain tissue.
The embryo, which begins as a flat sheet of cells, begins to acquire a cylindrical shape through the process of **embryonic folding**. The embryo folds laterally and again at either end, forming a C-shape with distinct head and tail ends. The embryo envelops a portion of the yolk sac, which protrudes with the umbilical cord from what will become the abdomen. The folding essentially creates a tube, called the primitive gut, that is lined by the endoderm. The amniotic sac, which was sitting on top of the flat embryo, envelops the embryo as it folds.
Within the first 8 weeks of gestation, a developing embryo establishes the rudimentary structures of all of its organs and tissues from the ectoderm, mesoderm, and endoderm. This process is called **organogenesis**.

Like the central nervous system, the heart also begins its development in the embryo as a tube-like structure, connected via capillaries to the chorionic villi. Cells of the primitive tube-shaped heart are capable of electrical conduction and contraction. The heart begins beating in the beginning of the fourth week, although it does not actually pump embryonic blood until a week later, when the oversized liver has begun producing red blood cells. (This is a temporary responsibility of the embryonic liver that the bone marrow will assume during fetal development.) During weeks 4–5, the eye pits form, limb buds become apparent, and the rudiments of the pulmonary system are formed.
During the sixth week, uncontrolled fetal limb movements begin to occur. The gastrointestinal system develops too rapidly for the embryonic abdomen to accommodate it, and the intestines temporarily loop into the umbilical cord. Paddle-shaped hands and feet develop fingers and toes by the process of apoptosis (programmed cell death), which causes the tissues between the fingers to disintegrate.

By week 7, the facial structure is more complex and includes nostrils, outer ears, and lenses. By the eighth week, the head is nearly as large as the rest of the embryo’s body, and all major brain structures are in place. The external genitalia are apparent, but at this point, there is no distinguishable difference between an embryo with egg producing and conducting (EPC) organs and one with sperm producing and conducting (SPC) organs. Bone begins to replace cartilage in the embryonic skeleton through the process of ossification. By the end of the embryonic period, the embryo is approximately 3 cm (1.2 in) from crown to rump and weighs approximately 8 g (0.25 oz).

Chapter Review

As the zygote travels toward the uterus, it undergoes numerous cleavages in which the number of cells doubles (blastomeres). Upon reaching the uterus, the conceptus has become a tightly packed sphere of cells called the morula, which then forms into a blastocyst consisting of an inner cell mass within a fluid-filled cavity surrounded by trophoblasts. The blastocyst implants in the uterine wall, the trophoblasts fuse to form a syncytiotrophoblast, and the conceptus is enveloped by the endometrium. Four embryonic membranes form to support the growing embryo: the amnion, the yolk sac, the allantois, and the chorion. The chorionic villi of the chorion extend into the endometrium to form the fetal portion of the placenta. The placenta supplies the growing embryo with oxygen and nutrients; it also removes carbon dioxide and other metabolic wastes.

Following implantation, embryonic cells undergo gastrulation, in which they differentiate and separate into an embryonic disc and establish three primary germ layers (the endoderm, mesoderm, and ectoderm). Through the process of embryonic folding, the fetus begins to take shape. Neurulation starts the process of the development of structures of the central nervous system and organogenesis establishes the basic plan for all organ systems.

Self Check

Answer the question(s) below to see how well you understand the topics covered in the previous section.

Critical Thinking Questions

Approximately 3 weeks after their last menstrual period, a sexually active person with EPC organs experiences a brief episode of abdominopelvic cramping and minor bleeding. What might be the explanation?

The Food and Nutrition Board of the Institute of Medicine recommends that all individuals who
might become pregnant consume at least 400 µg/day of folate from supplements or fortified foods. Why?
Fetal Development

Learning Objectives

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

- Differentiate between the embryonic period and the fetal period
- Briefly describe the process of the development of egg and sperm producing and conducting (EPC & SPC) organs
- Describe the fetal circulatory system and explain the role of the shunts
- Trace the development of a fetus from the end of the embryonic period to birth

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

Differentiation of EPC organs and SPC Organs

Differentiation does not begin until the fetal period, during weeks 9-12. Embryos of those with EPC organs and SPC organs, though genetically distinguishable, are morphologically identical. Bipotent gonads, or gonads that can develop into EPC organs or SPC organs, are connected to a central cavity called the cloaca via Müllerian ducts and Wolffian ducts. (The cloaca is an extension of the primitive gut.) Several events lead to differentiation during this period.

During the development of a fetus with SPC organs, the bipotent gonads become the testes and associated epididymis. The Müllerian ducts degenerate. The Wolffian ducts become the vas deferens, and the cloaca becomes the urethra and rectum.

During the development of a fetus with EPC organs, the bipotent gonads develop into ovaries. The Wolffian ducts degenerate. The Müllerian ducts become the uterine tubes and uterus, and the cloaca divides and develops into a vagina, a urethra, and a rectum.
Figure 1. Differentiation of EPC organs and SPC organs does not occur until the fetal period of development.
The Fetal Circulatory System

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

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

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

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

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

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

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

Developmental weeks 21–30 are characterized by rapid weight gain, which is important for maintaining a stable
body temperature after birth. The bone marrow completely takes over erythrocyte synthesis, and the axons of the spinal cord begin to be myelinated, or coated in the electrically insulating glial cell sheaths that are necessary for efficient nervous system functioning. (The process of myelination is not completed until adolescence.) During this period, the fetus grows eyelashes. The eyelids are no longer fused and can be opened and closed. The lungs begin producing surfactant, a substance that reduces surface tension in the lungs and assists proper lung expansion after birth. Inadequate surfactant production in premature newborns may result in respiratory distress syndrome, and as a result, the newborn may require surfactant replacement therapy, supplemental oxygen, or maintenance in a continuous positive airway pressure (CPAP) chamber during their first days or weeks of life. In male fetuses, the testes descend into the scrotum near the end of this period. The fetus at 30 weeks measures 28 cm (11 in) from crown to rump and exhibits the approximate body proportions of a full-term newborn, but still is much leaner.

Practice Questions
Visit the online OER to click the link here for a summary of the stages of pregnancy, as experienced by the gestational parent, and view the stages of development of the fetus throughout gestation. At what point in fetal development can a regular heartbeat be detected?

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

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

The passage of meconium in the uterus signals fetal distress, particularly fetal hypoxia (i.e., oxygen deprivation). This may be caused by maternal drug abuse (especially tobacco or cocaine), maternal hypertension, depletion of amniotic fluid, long labor or difficult birth, or a defect in the placenta that prevents it from delivering adequate oxygen to the fetus. Meconium passage is typically a complication of full-term or post-term newborns because it is rarely passed before 34 weeks of gestation, when the gastrointestinal system has matured and is appropriately controlled by nervous system stimuli. Fetal distress can stimulate the vagus nerve to trigger gastrointestinal peristalsis and relaxation of the anal sphincter. Notably, fetal hypoxic stress also induces a gasping reflex, increasing the likelihood that meconium will be inhaled into the fetal lungs. Although meconium is a sterile substance, it interferes with the antibiotic properties of the amniotic fluid and makes the newborn and mother more vulnerable to bacterial infections at birth and during the perinatal period. Specifically, inflammation of the fetal membranes, inflammation of the uterine lining, or neonatal sepsis (infection in the newborn) may occur. Meconium also irritates delicate fetal skin and can cause a rash.

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

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

The fetal period lasts from the ninth week of development until birth. During this period, EPC and SPC organs differentiate. The fetal circulatory system becomes much more specialized and efficient than its embryonic counterpart. It includes three shunts—the ductus venosus, the foramen ovale, and the ductus arteriosus—that enable it to bypass the semifunctional liver and pulmonary circuit until after childbirth. The brain continues to grow and its structures differentiate. Facial features develop, the body elongates, and the skeleton ossifies. In the womb, the developing fetus moves, blinks, practices sucking, and circulates amniotic fluid. The fetus grows from an embryo measuring approximately 3.3 cm (1.3 in) and weighing 7 g (0.25 oz) to an infant measuring approximately 51 cm (20 in) and weighing an average of approximately 3.4 kg (7.5 lbs). Embryonic organ structures that were primitive and nonfunctional develop to the point that the newborn can survive in the outside world.

Self Check

Answer the question(s) below to see how well you understand the topics covered in the previous section.

Critical Thinking Questions

What is the physiological benefit of incorporating shunts into the fetal circulatory system?

Why would a premature infant require supplemental oxygen?

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Gestational Parent Changes During Pregnancy, Labor, and Birth

Learning Objectives

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

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

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

Figure 1. The uterus grows throughout
Effects of Hormones

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

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

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

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

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

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

Weight Gain

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

During the first trimester, there’s no need to consume additional calories to maintain a healthy pregnancy. However, a weight gain of approximately 0.45 kg (1 lb) per month is common. During the second and third
trimesters, a pregnant individual’s appetite increases, but it is only necessary to consume an additional 300 calories per day to support the growing fetus. Most individuals gain approximately 0.45 kg (1 lb) per week.

| Table 1. Contributors to Weight Gain During Pregnancy |
|---------------------------------------------|-----------|-----------|
| Component                              | Weight (kg) | Weight (lb) |
| Fetus                                  | 3.2–3.6    | 7–8       |
| Placenta and fetal membranes           | 0.9–1.8    | 2–4       |
| Amniotic fluid                         | 0.9–1.4    | 2–3       |
| Breast tissue                          | 0.9–1.4    | 2–3       |
| Blood                                  | 1.4        | 4         |
| Fat                                    | 0.9–4.1    | 3–9       |
| Uterus                                 | 0.9–2.3    | 2–5       |
| Total                                  | 10–16.3    | 22–36     |

Changes in Organ Systems During Pregnancy

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

Digestive and Urinary System Changes

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

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

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

Circulatory System Changes

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

During the second half of pregnancy, the respiratory minute volume (volume of gas inhaled or exhaled by the lungs per minute) increases by 50 percent to compensate for the oxygen demands of the fetus and the increased parental metabolic rate. The growing uterus exerts upward pressure on the diaphragm, decreasing the volume of each inspiration and potentially causing shortness of breath, or dyspnea. During the last several weeks of pregnancy, the pelvis becomes more elastic, and the fetus descends lower in a process called **lightening**. This typically ameliorates dyspnea.

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

Integumentary System Changes

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

An increase in melanocyte-stimulating hormone, in conjunction with estrogens, darkens the areolae and creates a line of pigment from the umbilicus to the pubis called the linea nigra (Figure 2). Melanin production during pregnancy may also darken or discolor skin on the face to create a chloasma, or “mask of pregnancy.”

Physiology of Labor

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

First, recall that progesterone inhibits uterine contractions throughout the first several months of pregnancy. As the pregnancy enters its seventh month, progesterone levels plateau and then drop. Estrogen levels, however, continue to rise in the parental circulation. The increasing ratio of estrogen to progesterone makes the myometrium (the uterine smooth muscle) more sensitive to stimuli that promote contractions (because progesterone no longer inhibits them). Moreover, in the eighth month of pregnancy, fetal cortisol rises, which boosts estrogen secretion by the placenta and further overpowers the uterine-calming effects of progesterone. Some individuals may feel the result of the decreasing levels of progesterone in late pregnancy as weak and irregular peristaltic **Braxton Hicks contractions**, also called false labor. These contractions can often be relieved with rest or hydration.
Figure 3. A positive feedback loop of hormones works to initiate labor.

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

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

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

Stages of Childbirth

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

Cervical Dilation

For vaginal birth to occur, the cervix must dilate fully to 10 cm in diameter—wide enough to deliver the newborn’s head. The dilation stage is the longest stage of labor and typically takes 6–12 hours. However, it varies widely and may take minutes, hours, or days, depending in part on whether the individual has given birth before; in each subsequent labor, this stage tends to be shorter.
True labor progresses in a positive feedback loop in which uterine contractions stretch the cervix, causing it to dilate and efface, or become thinner. Cervical stretching induces reflexive uterine contractions that dilate and efface the cervix further. In addition, cervical dilation boosts oxytocin secretion from the pituitary, which in turn triggers more powerful uterine contractions. When labor begins, uterine contractions may occur only every 3–30 minutes and last only 20–40 seconds; however, by the end of this stage, contractions may occur as frequently as every 1.5–2 minutes and last for a full minute.

Each contraction sharply reduces oxygenated blood flow to the fetus. For this reason, it is critical that a period of relaxation occur after each contraction. Fetal distress, measured as a sustained decrease or increase in the fetal heart rate, can result from severe contractions that are too powerful or lengthy for oxygenated blood to be restored to the fetus. Such a situation can be cause for an emergency birth with vacuum, forceps, or surgically by Caesarian section.
The amniotic membranes rupture before the onset of labor in about 12 percent of women; they typically rupture at the end of the dilation stage in response to excessive pressure from the fetal head entering the birth canal.

**Expulsion Stage**

The *expulsion* stage begins when the fetal head enters the birth canal and ends with birth of the newborn. It typically takes up to 2 hours, but it can last longer or be completed in minutes, depending in part on the orientation of the fetus. The vertex presentation known as the occiput anterior vertex is the most common presentation and is associated with the greatest ease of vaginal birth. The fetus faces the parental spinal cord and the smallest part of the head (the posterior aspect called the occiput) exits the birth canal first.

In fewer than 5 percent of births, the infant is oriented in the breech presentation, or buttocks down. In a complete breech, both legs are crossed and oriented downward. In a frank breech presentation, the legs are oriented upward. Before the 1960s, it was common for breech presentations to be delivered vaginally. Today, most breech births are accomplished by Caesarian section.

Vaginal birth is associated with significant stretching of the vaginal canal, the cervix, and the perineum. Until recent decades, it was routine procedure for an obstetrician to numb the perineum and perform an episiotomy, an incision in the posterior vaginal wall and perineum. The perineum is now more commonly allowed to tear on its own during birth. Both an episiotomy and a perineal tear need to be sutured shortly after birth to ensure optimal healing. Although suturing the jagged edges of a perineal tear may be more difficult than suturing an episiotomy, tears heal more quickly, are less painful, and are associated with less damage to the muscles around the vagina and rectum.

Upon birth of the newborn’s head, an obstetrician will aspirate mucus from the mouth and nose before the newborn’s first breath. Once the head is birthed, the rest of the body usually follows quickly. The umbilical cord is then double-clamped, and a cut is made between the clamps. This completes the second stage of childbirth.

**Afterbirth**

The delivery of the placenta and associated membranes, commonly referred to as the *afterbirth*, marks the final stage of childbirth. After expulsion of the newborn, the myometrium continues to contract. This movement shears the placenta from the back of the uterine wall. It is then easily delivered through the vagina. Continued uterine contractions then reduce blood loss from the site of the placenta. Delivery of the placenta marks the beginning of the postpartum period—the period of approximately 6 weeks immediately following childbirth during which the parent’s body gradually returns to a non-pregnant state. If the placenta does not birth spontaneously within approximately 30 minutes, it is considered retained, and the obstetrician may attempt manual removal. If this is not successful, surgery may be required.

It is important that the obstetrician examines the expelled placenta and fetal membranes to ensure that they are intact. If fragments of the placenta remain in the uterus, they can cause postpartum hemorrhage. Uterine contractions continue for several hours after birth to return the uterus to its pre-pregnancy size in a process called involution, which also allows the parent’s abdominal organs to return to their pre-pregnancy locations. Breastfeeding facilitates this process.

Although postpartum uterine contractions limit blood loss from the detachment of the placenta, the parent does experience a postpartum vaginal discharge called lochia. This is made up of uterine lining cells, erythrocytes, leukocytes, and other debris. Thick, dark, lochia rubra (red lochia) typically continues for 2–3 days, and is replaced by lochia serosa, a thinner, pinkish form that continues until about the tenth postpartum day. After this period, a scant, creamy, or watery discharge called lochia alba (white lochia) may continue for another 1–2 weeks.

**Chapter Review**

Hormones (especially estrogens, progesterone, and hCG) secreted by the corpus luteum and later by the placenta are responsible for most of the changes experienced during pregnancy. Estrogen maintains the pregnancy, promotes fetal viability, and stimulates tissue growth in the parent and developing fetus. Progesterone prevents new ovarian follicles from developing and suppresses uterine contractility.
Pregnancy weight gain primarily occurs in the breasts and abdominal region. Nausea, heartburn, and frequent urination are common during pregnancy. Gestational parent blood volume increases by 30 percent during pregnancy and respiratory minute volume increases by 50 percent. The skin may develop stretch marks and melanin production may increase.

Toward the late stages of pregnancy, a drop in progesterone and stretching forces from the fetus lead to increasing uterine irritability and prompt labor. Contractions serve to dilate the cervix and expel the newborn. Delivery of the placenta and associated fetal membranes follows.

Self Check

Answer the question(s) below to see how well you understand the topics covered in the previous section.

Critical Thinking Questions

Devin is 35 weeks pregnant with their first child when they arrive at the birthing unit reporting that they believe they are in labor. They state that they have been experiencing diffuse, mild contractions for the past few hours. Examination reveals, however, that the plug of mucus blocking their cervix is intact and their cervix has not yet begun to dilate. Devin is advised to return home. Why?

Janine is 41 weeks pregnant with her first child when she arrives at the birthing unit reporting that she believes she has been in labor “for days” but that “it’s just not going anywhere.” During the clinical exam, she experiences a few mild contractions, each lasting about 15–20 seconds; however, her cervix is found to be only 2 cm dilated, and the amniotic sac is intact. Janine is admitted to the birthing unit and an IV infusion of pitocin is started. Why?
Adjustments of the Infant at Birth and Postnatal Stages

Learning Objectives

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

- Discuss the importance of an infant’s first breath
- Explain the closing of the cardiac shunts
- Describe thermoregulation in the newborn
- Summarize the importance of intestinal flora in the newborn

From a fetal perspective, the process of birth is a crisis. In the womb, the fetus was snuggled in a soft, warm, dark, and quiet world. The placenta provided nutrition and oxygen continuously. Suddenly, the contractions of labor and vaginal childbirth forcibly squeeze the fetus through the birth canal, limiting oxygenated blood flow during contractions and shifting the skull bones to accommodate the small space. After birth, the newborn’s system must make drastic adjustments to a world that is colder, brighter, and louder, and where they will experience hunger and thirst. The neonatal period (neo- = “new”; -natal = “birth”) spans the first to the thirtieth day of life outside of the uterus.

Respiratory Adjustments

Although the fetus “practices” breathing by inhaling amniotic fluid in utero, there is no air in the uterus and thus no true opportunity to breathe. (There is also no need to breathe because the placenta supplies the fetus with all the oxygenated blood it needs.) During gestation, the partially collapsed lungs are filled with amniotic fluid and exhibit very little metabolic activity. Several factors stimulate newborns to take their first breath at birth. First, labor contractions temporarily constrict umbilical blood vessels, reducing oxygenated blood flow to the fetus and elevating carbon dioxide levels in the blood. High carbon dioxide levels cause acidosis and stimulate the respiratory center in the brain, triggering the newborn to take a breath.

The first breath typically is taken within 10 seconds of birth, after mucus is aspirated from the infant’s mouth and nose. The first breaths inflate the lungs to nearly full capacity and dramatically decrease lung pressure and resistance to blood flow, causing a major circulatory reconfiguration. Pulmonary alveoli open, and alveolar capillaries fill with blood. Amniotic fluid in the lungs drains or is absorbed, and the lungs immediately take over the task of the placenta, exchanging carbon dioxide for oxygen by the process of respiration.

Circulatory Adjustments

The process of clamping and cutting the umbilical cord collapses the umbilical blood vessels. In the absence of medical assistance, this occlusion would occur naturally within 20 minutes of birth because the Wharton’s jelly within the umbilical cord would swell in response to the lower temperature outside of the mother’s body, and the blood vessels would constrict. Natural occlusion has occurred when the umbilical cord is no longer pulsating. For the most part, the collapsed vessels atrophy and become fibrotic remnants, existing in the mature circulatory system as ligaments of the abdominal wall and liver. The ductus venosus degenerates to become the ligamentum
venousum beneath the liver. Only the proximal sections of the two umbilical arteries remain functional, taking on the role of supplying blood to the upper part of the bladder.

The newborn’s first breath is vital to initiate the transition from the fetal to the neonatal circulatory pattern. Inflation of the lungs decreases blood pressure throughout the pulmonary system, as well as in the right atrium and ventricle. In response to this pressure change, the flow of blood temporarily reverses direction through the foramen ovale, moving from the left to the right atrium, and blocking the shunt with two flaps of tissue. Within 1 year, the tissue flaps usually fuse over the shunt, turning the foramen ovale into the fossa ovalis. The ductus arteriosus constricts as a result of increased oxygen concentration, and becomes the ligamentum arteriosum. Closing of the ductus arteriosus ensures that all blood pumped to the pulmonary circuit will be oxygenated by the newly functional neonatal lungs.

**Thermoregulatory Adjustments**

The fetus floats in warm amniotic fluid that is maintained at a temperature of approximately 98.6°F with very little fluctuation. Birth exposes newborns to a cooler environment in which they have to regulate their own body temperature. Newborns have a higher ratio of surface area to volume than adults. This means that their body has less volume throughout which to produce heat, and more surface area from which to lose heat. As a result, newborns produce heat more slowly and lose it more quickly. Newborns also have immature musculature that limits their ability to generate heat by shivering. Moreover, their nervous systems are underdeveloped, so they cannot quickly constrict superficial blood vessels in response to cold. They also have little subcutaneous fat for insulation. All these factors make it harder for newborns to maintain their body temperature.

Newborns, however, do have a special method for generating heat: **nonshivering thermogenesis**, which involves the breakdown of **brown adipose tissue**, or brown fat, which is distributed over the back, chest, and shoulders. Brown fat differs from the more familiar white fat in two ways:
Anatomy

- It is highly vascularized. This allows for faster delivery of oxygen, which leads to faster cellular respiration.
- It is packed with a special type of mitochondria that are able to engage in cellular respiration reactions that produce less ATP and more heat than standard cellular respiration reactions.

The breakdown of brown fat occurs automatically upon exposure to cold, so it is an important heat regulator in newborns. During fetal development, the placenta secretes inhibitors that prevent metabolism of brown adipose fat and promote its accumulation in preparation for birth.

Gastrointestinal and Urinary Adjustments

In adults, the gastrointestinal tract harbors bacterial flora—trillions of bacteria that aid in digestion, produce vitamins, and protect from the invasion or replication of pathogens. In stark contrast, the fetal intestine is sterile. The first consumption of breast milk or formula floods the neonatal gastrointestinal tract with beneficial bacteria that begin to establish the bacterial flora.

The fetal kidneys filter blood and produce urine, but the neonatal kidneys are still immature and inefficient at concentrating urine. Therefore, newborns produce very dilute urine, making it particularly important for infants to obtain sufficient fluids from breast milk or formula.

Homeostatic Imbalances: Apgar Score

In the minutes following birth, a newborn must undergo dramatic systemic changes to be able to survive outside the womb. An obstetrician, midwife, or nurse can estimate how well a newborn is doing by obtaining an Apgar score. The Apgar score was introduced in 1952 by the anesthesiologist Dr. Virginia Apgar as a method to assess the effects on the newborn of anesthesia given to the laboring mother. Healthcare providers now use it to assess the general wellbeing of the newborn, whether or not analgesics or anesthetics were used. Five criteria—skin color, heart rate, reflex, muscle tone, and respiration—are assessed, and each criterion is assigned a score of 0, 1, or 2. Scores are taken at 1 minute after birth and again at 5 minutes after birth. Each time that scores are taken, the five scores are added together. High scores (out of a possible 10) indicate the baby has made the transition from the womb well, whereas lower scores indicate that the baby may be in distress.

The technique for determining an Apgar score is quick and easy, painless for the newborn, and does not require any instruments except for a stethoscope. A convenient way to remember the five scoring criteria is to apply the mnemonic APGAR, for “appearance” (skin color), “pulse” (heart rate), “grimace” (reflex), “activity” (muscle tone), and “respiration.”

Of the five Apgar criteria, heart rate and respiration are the most critical. Poor scores for either of these measurements may indicate the need for immediate medical attention to resuscitate or stabilize the newborn. In general, any score lower than 7 at the 5-minute mark indicates that medical assistance may be needed. A total score below 5 indicates an emergency situation. Normally, a newborn will get an intermediate score of 1 for some of the Apgar criteria and will progress to a 2 by the 5-minute assessment. Scores of 8 or above are normal.

Chapter Review

The first breath a newborn takes at birth inflates the lungs and dramatically alters the circulatory system, closing the three shunts that directed oxygenated blood away from the lungs and liver during fetal life. Clamping and cutting the umbilical cord collapses the three umbilical blood vessels. The proximal umbilical arteries remain a part of the circulatory system, whereas the distal umbilical arteries and the umbilical vein become fibrotic. The newborn keeps warm by breaking down brown adipose tissue in the process of nonshivering thermogenesis. The first consumption of breast milk or formula floods the newborn’s sterile gastrointestinal tract with beneficial bacteria that eventually establish themselves as the bacterial flora, which aid in digestion.
Self Check

Answer the question(s) below to see how well you understand the topics covered in the previous section.

Critical Thinking Questions

Describe how the newborn’s first breath alters the circulatory pattern.
Newborns are at much higher risk for dehydration than adults. Why?

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Lactation

Learning Objectives

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

- Describe the structure of the lactating breast
- Summarize the process of lactation
- Explain how the composition of breast milk changes during the first days of lactation and in the course of a single feeding

Lactation is the process by which milk is synthesized and secreted from the mammary glands of the postpartum breast in response to an infant sucking at the nipple. Breast milk provides ideal nutrition and passive immunity for the infant, encourages mild uterine contractions to return the uterus to its pre-pregnancy size (i.e., involution), and induces a substantial metabolic increase in the parent, consuming the fat reserves stored during pregnancy.

Structure of the Lactating Breast

Mammary glands are modified sweat glands. The non-pregnant and non-lactating breast is composed primarily of adipose and collagenous tissue, with mammary glands making up a very minor proportion of breast volume. The mammary gland is composed of milk-transporting lactiferous ducts, which expand and branch extensively during pregnancy in response to estrogen, growth hormone, cortisol, and prolactin. Moreover, in response to progesterone, clusters of breast alveoli bud from the ducts and expand outward toward the chest wall. Breast alveoli are balloon-like structures lined with milk-secreting cuboidal cells, or lactocytes, that are surrounded by a net of contractile myoepithelial cells. Milk is secreted from the lactocytes, fills the alveoli, and is squeezed into the ducts. Clusters of alveoli that drain to a common duct are called lobules; the lactating individual has 12-20 lobules organized radially around the nipple. Milk drains from lactiferous ducts into lactiferous sinuses that meet at 4 to 18 perforations in the nipple, called nipple pores. The small bumps of the areola (the darkened skin around the nipple) are called Montgomery glands. They secrete oil to cleanse the nipple opening and prevent chapping and cracking of the nipple during breastfeeding.

The Process of Lactation

The pituitary hormone prolactin is instrumental in the establishment and maintenance of breast milk supply. It also is important for the mobilization of parental micronutrients for breast milk.

Near the fifth week of pregnancy, the level of circulating prolactin begins to increase, eventually rising to approximately 10-20 times the pre-pregnancy concentration. We noted earlier that, during pregnancy, prolactin and other hormones prepare the breasts anatomically for the secretion of milk. The level of prolactin plateaus in late pregnancy, at a level high enough to initiate milk production. However, estrogen, progesterone, and other placental hormones inhibit prolactin-mediated milk synthesis during pregnancy. It is not until the placenta is expelled that this inhibition is lifted and milk production commences.

After childbirth, the baseline prolactin level drops sharply, but it is restored for a 1-hour spike during each feeding to stimulate the production of milk for the next feeding. With each prolactin spike, estrogen and progesterone also increase slightly.
Anatomy

When the infant suckles, sensory nerve fibers in the areola trigger a neuroendocrine reflex that results in milk secretion from lactocytes into the alveoli. The posterior pituitary releases oxytocin, which stimulates myoepithelial cells to squeeze milk from the alveoli so it can drain into the lactiferous ducts, collect in the lactiferous sinuses, and discharge through the nipple pores. It takes less than 1 minute from the time when an infant begins suckling (the latent period) until milk is secreted (the let-down). The image below summarizes the positive feedback loop of the let-down reflex.

The prolactin-mediated synthesis of milk changes with time. Frequent milk removal by breastfeeding (or pumping) will maintain high circulating prolactin levels for several months. However, even with continued breastfeeding, baseline prolactin will decrease over time to its pre-pregnancy level. In addition to prolactin and oxytocin, growth hormone, cortisol, parathyroid hormone, and insulin contribute to lactation, in part by facilitating the transport of maternal amino acids, fatty acids, glucose, and calcium to breast milk.
Changes in the Composition of Breast Milk

In the final weeks of pregnancy, the alveoli swell with colostrum, a thick, yellowish substance that is high in protein but contains less fat and glucose than mature breast milk. Before childbirth, some individuals experience leakage of colostrum from the nipples. In contrast, mature breast milk does not leak during pregnancy and is not secreted until several days after childbirth.

| Table 1. Compositions of Human Colostrum, Mature Breast Milk, and Cow’s Milk (g/L) |
|----------------------------------|----------------------------------|----------------------------------|
|                                  | Human colostrum | Human breast milk | Cow’s milk*                    |
| Total protein                    | 23              | 11                | 31                              |
| Immunoglobulins                  | 19              | 0.1               | 1                               |
| Fat                              | 30              | 45                | 38                              |
| Lactose                          | 57              | 71                | 47                              |
| Calcium                          | 0.5             | 0.3               | 1.4                             |
| Phosphorus                       | 0.16            | 0.14              | 0.90                            |
| Sodium                           | 0.50            | 0.15              | 0.41                            |

*Cow’s milk should never be given to an infant. Its composition is not suitable and its proteins are difficult for the infant to digest.

Colostrum is secreted during the first 48–72 hours postpartum. Only a small volume of colostrum is produced—approximately 3 ounces in a 24-hour period—but it is sufficient for the newborn in the first few days of life. Colostrum is rich with immunoglobulins, which confer gastrointestinal, and also likely systemic, immunity as the newborn adjusts to a nonsterile environment.

After about the third postpartum day, the mother secretes transitional milk that represents an intermediate between mature milk and colostrum. This is followed by mature milk from approximately postpartum day 10. As you can see in the accompanying table, cow’s milk is not a substitute for breast milk. It contains less lactose, less fat, and more protein and minerals. Moreover, the proteins in cow’s milk are difficult for an infant’s immature digestive system to metabolize and absorb.

The first few weeks of breastfeeding may involve leakage, soreness, and periods of milk engorgement as the relationship between milk supply and infant demand becomes established. Once this period is complete, the parent will produce approximately 1.5 liters of milk per day for a single infant, and more if there are twins or triplets. As the infant goes through growth spurts, the milk supply constantly adjusts to accommodate changes in demand. An individual can continue to lactate for years, but once breastfeeding is stopped for approximately 1 week, any remaining milk will be reabsorbed; in most cases, no more will be produced, even if suckling or pumping is resumed.

Mature milk changes from the beginning to the end of a feeding. The early milk, called foremilk, is watery, translucent, and rich in lactose and protein. Its purpose is to quench the infant’s thirst. Hindmilk is delivered toward the end of a feeding. It is opaque, creamy, and rich in fat, and serves to satisfy the infant’s appetite.

During the first days of a newborn’s life, it is important for meconium to be cleared from the intestines and for bilirubin to be kept low in the circulation. Recall that bilirubin, a product of erythrocyte breakdown, is processed by the liver and secreted in bile. It enters the gastrointestinal tract and exits the body in the stool. Breast milk has laxative properties that help expel meconium from the intestines and clear bilirubin through the excretion of bile.
A high concentration of bilirubin in the blood causes jaundice. Some degree of jaundice is normal in newborns, but a high level of bilirubin—which is neurotoxic—can cause brain damage. Newborns, who do not yet have a fully functional blood–brain barrier, are highly vulnerable to the bilirubin circulating in the blood. Indeed, hyperbilirubinemia, a high level of circulating bilirubin, is the most common condition requiring medical attention in newborns. Newborns with hyperbilirubinemia are treated with phototherapy because UV light helps to break down the bilirubin quickly.

Chapter Review

The lactating parent supplies all the hydration and nutrients that a growing infant needs for the first 4–6 months of life. During pregnancy, the body prepares for lactation by stimulating the growth and development of branching lactiferous ducts and alveoli lined with milk-secreting lactocytes, and by creating colostrum. These functions are attributable to the actions of several hormones, including prolactin. Following childbirth, suckling triggers oxytocin release, which stimulates myoepithelial cells to squeeze milk from alveoli. Breast milk then drains toward the nipple pores to be consumed by the infant. Colostrum, the milk produced in the first postpartum days, provides immunoglobulins that increase the newborn’s immune defenses. Colostrum, transitional milk, and mature breast milk are ideally suited to each stage of the newborn’s development, and breastfeeding helps the newborn’s digestive system expel meconium and clear bilirubin. Mature milk changes from the beginning to the end of a feeding. Foremilk quenches the infant’s thirst, whereas hindmilk satisfies the infant’s appetite.

Self Check

Answer the question(s) below to see how well you understand the topics covered in the previous section.

Critical Thinking Questions

Describe the transit of breast milk from lactocytes to nipple pores.
A person who stopped breastfeeding suddenly is experiencing breast engorgement and leakage, just like they did in the first few weeks of breastfeeding. Why?

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Glossary
Glossary Section 16

Glossary: Blood

**albumin**: most abundant plasma protein, accounting for most of the osmotic pressure of plasma

**antibodies**: (also, immunoglobulins or gamma globulins) antigen-specific proteins produced by specialized B lymphocytes that protect the body by binding to foreign objects such as bacteria and viruses

**blood**: liquid connective tissue composed of formed elements—erythrocytes, leukocytes, and platelets—and a fluid extracellular matrix called plasma; component of the cardiovascular system

**buffy coat**: thin, pale layer of leukocytes and platelets that separates the erythrocytes from the plasma in a sample of centrifuged blood

**fibrinogen**: plasma protein produced in the liver and involved in blood clotting

**formed elements**: cellular components of blood; that is, erythrocytes, leukocytes, and platelets

**globulins**: heterogeneous group of plasma proteins that includes transport proteins, clotting factors, immune proteins, and others

**hematocrit**: (also, packed cell volume) volume percentage of erythrocytes in a sample of centrifuged blood

**immunoglobulins**: (also, antibodies or gamma globulins) antigen-specific proteins produced by specialized B lymphocytes that protect the body by binding to foreign objects such as bacteria and viruses

**packed cell volume (PCV)**: (also, hematocrit) volume percentage of erythrocytes present in a sample of centrifuged blood

**plasma**: in blood, the liquid extracellular matrix composed mostly of water that circulates the formed elements and dissolved materials throughout the cardiovascular system

**platelets**: (also, thrombocytes) one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes

**red blood cells (RBCs)**: (also, erythrocytes) one of the formed elements of blood that transports oxygen

**white blood cells (WBCs)**: (also, leukocytes) one of the formed elements of blood that provides defense against disease agents and foreign materials

Glossary: Erythrocytes

**anemia**: deficiency of red blood cells or hemoglobin

**bilirubin**: yellowish bile pigment produced when iron is removed from heme and is further broken down into waste products

**biliverdin**: green bile pigment produced when the non-iron portion of heme is degraded into a waste product; converted to bilirubin in the liver
**Anatomy**

**Carbaminohemoglobin**: compound of carbon dioxide and hemoglobin, and one of the ways in which carbon dioxide is carried in the blood

**Deoxyhemoglobin**: molecule of hemoglobin without an oxygen molecule bound to it

**Erythrocyte**: (also, red blood cell) mature myeloid blood cell that is composed mostly of hemoglobin and functions primarily in the transportation of oxygen and carbon dioxide

**Ferritin**: protein-containing storage form of iron found in the bone marrow, liver, and spleen

**Globin**: heme-containing globular protein that is a constituent of hemoglobin

**Heme**: red, iron-containing pigment to which oxygen binds in hemoglobin

**Hemoglobin**: oxygen-carrying compound in erythrocytes

**Hemosiderin**: protein-containing storage form of iron found in the bone marrow, liver, and spleen

**Hypoxemia**: below-normal level of oxygen saturation of blood (typically <95 percent)

**Macrophage**: phagocytic cell of the myeloid lineage; a matured monocyte

**Oxyhemoglobin**: molecule of hemoglobin to which oxygen is bound

**Polycythemia**: elevated level of hemoglobin, whether adaptive or pathological

**Reticulocyte**: immature erythrocyte that may still contain fragments of organelles

**Sickle cell disease**: (also, sickle cell anemia) inherited blood disorder in which hemoglobin molecules are malformed, leading to the breakdown of RBCs that take on a characteristic sickle shape

**Thalassemia**: inherited blood disorder in which maturation of RBCs does not proceed normally, leading to abnormal formation of hemoglobin and the destruction of RBCs

**Transferrin**: plasma protein that binds reversibly to iron and distributes it throughout the body

**Glossary: Leukocytes & Platelets**

**Agranular leukocytes**: leukocytes with few granules in their cytoplasm; specifically, monocytes, lymphocytes, and NK cells

**B lymphocytes**: (also, B cells) lymphocytes that defend the body against specific pathogens and thereby provide specific immunity

**Basophils**: granulocytes that stain with a basic (alkaline) stain and store histamine and heparin

**Defensins**: antimicrobial proteins released from neutrophils and macrophages that create openings in the plasma membranes to kill cells

**Diapedesis**: (also, emigration) process by which leukocytes squeeze through adjacent cells in a blood vessel wall to enter tissues

**Emigration**: (also, diapedesis) process by which leukocytes squeeze through adjacent cells in a blood vessel wall to enter tissues

**Eosinophils**: granulocytes that stain with eosin; they release antihistamines and are especially active against parasitic worms

**Granular leukocytes**: leukocytes with abundant granules in their cytoplasm; specifically, neutrophils, eosinophils, and basophils
leukemia: cancer involving leukocytes

leukocyte: (also, white blood cell) colorless, nucleated blood cell, the chief function of which is to protect the body from disease

leukocytosis: excessive leukocyte proliferation

leukopenia: below-normal production of leukocytes

lymphocytes: agranular leukocytes of the lymphoid stem cell line, many of which function in specific immunity

lymphoma: form of cancer in which masses of malignant T and/or B lymphocytes collect in lymph nodes, the spleen, the liver, and other tissues

lysozyme: digestive enzyme with bactericidal properties

megakaryocyte: bone marrow cell that produces platelets

memory cell: type of B or T lymphocyte that forms after exposure to a pathogen

monocytes: agranular leukocytes of the myeloid stem cell line that circulate in the bloodstream; tissue monocytes are macrophages

natural killer (NK) cells: cytotoxic lymphocytes capable of recognizing cells that do not express “self” proteins on their plasma membrane or that contain foreign or abnormal markers; provide generalized, nonspecific immunity

neutrophils: granulocytes that stain with a neutral dye and are the most numerous of the leukocytes; especially active against bacteria

polymorphonuclear: having a lobed nucleus, as seen in some leukocytes

positive chemotaxis: process in which a cell is attracted to move in the direction of chemical stimuli

T lymphocytes: (also, T cells) lymphocytes that provide cellular-level immunity by physically attacking foreign or diseased cells

thrombocytes: platelets, one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes

thrombocytopenia: condition in which there are too few platelets, resulting in abnormal bleeding (hemophilia)

thrombocytosis: condition in which there are too many platelets, resulting in abnormal clotting (thrombosis)

Glossary: Blood Typing

ABO blood group: blood-type classification based on the presence or absence of A and B glycoproteins on the erythrocyte membrane surface

agglutination: clustering of cells into masses linked by antibodies

cross matching: blood test for identification of blood type using antibodies and small samples of blood

hemolysis: destruction (lysis) of erythrocytes and the release of their hemoglobin into circulation

hemolytic disease of the newborn (HDN): (also, erythroblastosis fetalis) disorder causing agglutination and hemolysis in an Rh+ fetus or newborn of an Rh− mother

Rh blood group: blood-type classification based on the presence or absence of the antigen Rh on the erythrocyte membrane surface

universal donor: individual with type O− blood
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**universal recipient**: individual with type AB* blood
**Glossary Section 17**

**Glossary: Heart Anatomy**

**anastomosis:** (plural = anastomoses) area where vessels unite to allow blood to circulate even if there may be partial blockage in another branch

**anterior cardiac veins:** vessels that parallel the small cardiac arteries and drain the anterior surface of the right ventricle; bypass the coronary sinus and drain directly into the right atrium

**anterior interventricular artery:** (also, left anterior descending artery or LAD) major branch of the left coronary artery that follows the anterior interventricular sulcus

**anterior interventricular sulcus:** sulcus located between the left and right ventricles on the anterior surface of the heart

**aortic valve:** (also, aortic semilunar valve) valve located at the base of the aorta

**atrioventricular septum:** cardiac septum located between the atria and ventricles; atrioventricular valves are located here

**atrioventricular valves:** one-way valves located between the atria and ventricles; the valve on the right is called the tricuspid valve, and the one on the left is the mitral or bicuspid valve

**atrium:** (plural = atria) upper or receiving chamber of the heart that pumps blood into the lower chambers just prior to their contraction; the right atrium receives blood from the systemic circuit that flows into the right ventricle; the left atrium receives blood from the pulmonary circuit that flows into the left ventricle

**auricle:** extension of an atrium visible on the superior surface of the heart

**bicuspid valve:** (also, mitral valve or left atrioventricular valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

**cardiac notch:** depression in the medial surface of the inferior lobe of the left lung where the apex of the heart is located

**cardiac skeleton:** (also, skeleton of the heart) reinforced connective tissue located within the atrioventricular septum; includes four rings that surround the openings between the atria and ventricles, and the openings to the pulmonary trunk and aorta; the point of attachment for the heart valves

**cardiomyocyte:** muscle cell of the heart

**chordae tendineae:** string-like extensions of tough connective tissue that extend from the flaps of the atrioventricular valves to the papillary muscles

**circumflex artery:** branch of the left coronary artery that follows coronary sulcus

**coronary arteries:** branches of the ascending aorta that supply blood to the heart; the left coronary artery feeds the left side of the heart, the left atrium and ventricle, and the interventricular septum; the right coronary artery feeds the right atrium, portions of both ventricles, and the heart conduction system

**coronary sinus:** large, thin-walled vein on the posterior surface of the heart that lies within the atrioventricular sulcus and drains the heart myocardium directly into the right atrium
**coronary sulcus**: sulcus that marks the boundary between the atria and ventricles

**coronary veins**: vessels that drain the heart and generally parallel the large surface arteries

**endocardium**: innermost layer of the heart lining the heart chambers and heart valves; composed of endothelium reinforced with a thin layer of connective tissue that binds to the myocardium

**endothelium**: layer of smooth, simple squamous epithelium that lines the endocardium and blood vessels

**epicardial coronary arteries**: surface arteries of the heart that generally follow the sulci

**epicardium**: innermost layer of the serous pericardium and the outermost layer of the heart wall

**foramen ovale**: opening in the fetal heart that allows blood to flow directly from the right atrium to the left atrium, bypassing the fetal pulmonary circuit

**fossa ovalis**: oval-shaped depression in the interatrial septum that marks the former location of the foramen ovale

**great cardiac vein**: vessel that follows the interventricular sulcus on the anterior surface of the heart and flows along the coronary sulcus into the coronary sinus on the posterior surface; parallels the anterior interventricular artery and drains the areas supplied by this vessel

**hypertrophic cardiomyopathy**: pathological enlargement of the heart, generally for no known reason

**inferior vena cava**: large systemic vein that returns blood to the heart from the inferior portion of the body

**interatrial septum**: cardiac septum located between the two atria; contains the fossa ovalis after birth

**interventricular septum**: cardiac septum located between the two ventricles

**left atrioventricular valve**: (also, mitral valve or bicuspid valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

**marginal arteries**: branches of the right coronary artery that supply blood to the superficial portions of the right ventricle

**mesothelium**: simple squamous epithelial portion of serous membranes, such as the superficial portion of the epicardium (the visceral pericardium) and the deepest portion of the pericardium (the parietal pericardium)

**middle cardiac vein**: vessel that parallels and drains the areas supplied by the posterior interventricular artery; drains into the great cardiac vein

**mitral valve**: (also, left atrioventricular valve or bicuspid valve) valve located between the left atrium and ventricle; consists of two flaps of tissue

**moderator band**: band of myocardium covered by endocardium that arises from the inferior portion of the interventricular septum in the right ventricle and crosses to the anterior papillary muscle; contains conductile fibers that carry electrical signals followed by contraction of the heart

**myocardium**: thickest layer of the heart composed of cardiac muscle cells built upon a framework of primarily collagenous fibers and blood vessels that supply it and the nervous fibers that help to regulate it

**papillary muscle**: extension of the myocardium in the ventricles to which the chordae tendineae attach

**pectinate muscles**: muscular ridges seen on the anterior surface of the right atrium

**pericardial cavity**: cavity surrounding the heart filled with a lubricating serous fluid that reduces friction as the heart contracts

**pericardial sac**: (also, pericardium) membrane that separates the heart from other mediastinal structures; consists of two distinct, fused sublayers: the fibrous pericardium and the parietal pericardium

**pericardium**: (also, pericardial sac) membrane that separates the heart from other mediastinal structures; consists of two distinct, fused sublayers: the fibrous pericardium and the parietal pericardium
**posterior cardiac vein**: vessel that parallels and drains the areas supplied by the marginal artery branch of the circumflex artery; drains into the great cardiac vein

**posterior interventricular artery**: (also, posterior descending artery) branch of the right coronary artery that runs along the posterior portion of the interventricular sulcus toward the apex of the heart and gives rise to branches that supply the interventricular septum and portions of both ventricles

**posterior interventricular sulcus**: sulcus located between the left and right ventricles on the anterior surface of the heart

**pulmonary arteries**: left and right branches of the pulmonary trunk that carry deoxygenated blood from the heart to each of the lungs

**pulmonary capillaries** capillaries surrounding the alveoli of the lungs where gas exchange occurs: carbon dioxide exits the blood and oxygen enters

**pulmonary circuit**: blood flow to and from the lungs

**pulmonary trunk**: large arterial vessel that carries blood ejected from the right ventricle; divides into the left and right pulmonary arteries

**pulmonary valve**: (also, pulmonary semilunar valve, the pulmonic valve, or the right semilunar valve) valve at the base of the pulmonary trunk that prevents backflow of blood into the right ventricle; consists of three flaps

**pulmonary veins**: veins that carry highly oxygenated blood into the left atrium, which pumps the blood into the left ventricle, which in turn pumps oxygenated blood into the aorta and to the many branches of the systemic circuit

**right atrioventricular valve**: (also, tricuspid valve) valve located between the right atrium and ventricle; consists of three flaps of tissue

**semilunar valves**: valves located at the base of the pulmonary trunk and at the base of the aorta

**septum**: (plural = septa) walls or partitions that divide the heart into chambers

**septum primum**: flap of tissue in the fetus that covers the foramen ovale within a few seconds after birth

**small cardiac vein**: parallels the right coronary artery and drains blood from the posterior surfaces of the right atrium and ventricle; drains into the great cardiac vein

**sulcus**: (plural = sulci) fat-filled groove visible on the surface of the heart; coronary vessels are also located in these areas

**superior vena cava**: large systemic vein that returns blood to the heart from the superior portion of the body

**systemic circuit**: blood flow to and from virtually all of the tissues of the body

**trabeculae carneae**: ridges of muscle covered by endocardium located in the ventricles

**tricuspid valve**: term used most often in clinical settings for the right atrioventricular valve

**valve**: in the cardiovascular system, a specialized structure located within the heart or vessels that ensures one-way flow of blood

**ventricle**: one of the primary pumping chambers of the heart located in the lower portion of the heart; the left ventricle is the major pumping chamber on the lower left side of the heart that ejects blood into the systemic circuit via the aorta and receives blood from the left atrium; the right ventricle is the major pumping chamber on the lower right side of the heart that ejects blood into the pulmonary circuit via the pulmonary trunk and receives blood from the right atrium
Glossary: Development of the Heart

**bulbus cordis**: portion of the primitive heart tube that will eventually develop into the right ventricle

**cardiogenic area**: area near the head of the embryo where the heart begins to develop 18–19 days after fertilization

**cardiogenic cords**: two strands of tissue that form within the cardiogenic area

**endocardial tubes**: stage in which lumens form within the expanding cardiogenic cords, forming hollow structures

**heart bulge**: prominent feature on the anterior surface of the heart, reflecting early cardiac development

**mesoderm**: one of the three primary germ layers that differentiate early in embryonic development

**primitive atrium**: portion of the primitive heart tube that eventually becomes the anterior portions of both the right and left atria, and the two auricles

**primitive heart tube**: singular tubular structure that forms from the fusion of the two endocardial tubes

**primitive ventricle**: portion of the primitive heart tube that eventually forms the left ventricle

**sinus venosus**: develops into the posterior portion of the right atrium, the SA node, and the coronary sinus

**truncus arteriosus**: portion of the primitive heart that will eventually divide and give rise to the ascending aorta and pulmonary trunk
Glossary Section 18

Glossary: Structure and Function of Blood Vessels

**arteriole:** (also, resistance vessel) very small artery that leads to a capillary

**arteriovenous anastomosis:** short vessel connecting an arteriole directly to a venule and bypassing the capillary beds

**artery:** blood vessel that conducts blood away from the heart; may be a conducting or distributing vessel

**capacitance:** ability of a vein to distend and store blood

**capacitance vessels:** veins

**capillary:** smallest of blood vessels where physical exchange occurs between the blood and tissue cells surrounded by interstitial fluid

**capillary bed:** network of 10–100 capillaries connecting arterioles to venules

**continuous capillary:** most common type of capillary, found in virtually all tissues except epithelia and cartilage; contains very small gaps in the endothelial lining that permit exchange

**elastic artery:** (also, conducting artery) artery with abundant elastic fibers located closer to the heart, which maintains the pressure gradient and conducts blood to smaller branches

**external elastic membrane:** membrane composed of elastic fibers that separates the tunica media from the tunica externa; seen in larger arteries

**fenestrated capillary:** type of capillary with pores or fenestrations in the endothelium that allow for rapid passage of certain small materials

**internal elastic membrane:** membrane composed of elastic fibers that separates the tunica intima from the tunica media; seen in larger arteries

**lumen:** interior of a tubular structure such as a blood vessel or a portion of the alimentary canal through which blood, chyme, or other substances travel

**metarteriole:** short vessel arising from a terminal arteriole that branches to supply a capillary bed

**microcirculation:** blood flow through the capillaries

**muscular artery:** (also, distributing artery) artery with abundant smooth muscle in the tunica media that branches to distribute blood to the arteriole network

**nervi vasorum:** small nerve fibers found in arteries and veins that trigger contraction of the smooth muscle in their walls

**perfusion:** distribution of blood into the capillaries so the tissues can be supplied

**precapillary sphincters:** circular rings of smooth muscle that surround the entrance to a capillary and regulate
blood flow into that capillary

**sinusoid capillary**: rarest type of capillary, which has extremely large intercellular gaps in the basement membrane in addition to clefts and fenestrations; found in areas such as the bone marrow and liver where passage of large molecules occurs

**thoroughfare channel**: continuation of the metarteriole that enables blood to bypass a capillary bed and flow directly into a venule, creating a vascular shunt

**tunica externa**: (also, tunica adventitia) outermost layer or tunic of a vessel (except capillaries)

**tunica intima**: (also, tunica interna) innermost lining or tunic of a vessel

**tunica media**: middle layer or tunic of a vessel (except capillaries)

**vasa vasorum**: small blood vessels located within the walls or tunics of larger vessels that supply nourishment to and remove wastes from the cells of the vessels

**vascular shunt**: continuation of the metarteriole and thoroughfare channel that allows blood to bypass the capillary beds to flow directly from the arterial to the venous circulation

**vasoconstriction**: constriction of the smooth muscle of a blood vessel, resulting in a decreased vascular diameter

**vasodilation**: relaxation of the smooth muscle in the wall of a blood vessel, resulting in an increased vascular diameter

**vasomotion**: irregular, pulsating flow of blood through capillaries and related structures

**vein**: blood vessel that conducts blood toward the heart

**venous reserve**: volume of blood contained within systemic veins in the integument, bone marrow, and liver that can be returned to the heart for circulation, if needed

**venule**: small vessel leading from the capillaries to veins

**Glossary: Circulatory Pathways**

**abdominal aorta**: portion of the aorta inferior to the aortic hiatus and superior to the common iliac arteries

**adrenal artery**: branch of the abdominal aorta; supplies blood to the adrenal (suprarenal) glands

**adrenal vein**: drains the adrenal or suprarenal glands that are immediately superior to the kidneys; the right adrenal vein enters the inferior vena cava directly and the left adrenal vein enters the left renal vein

**anterior cerebral artery**: arises from the internal carotid artery; supplies the frontal lobe of the cerebrum

**anterior communicating artery**: anastomosis of the right and left internal carotid arteries; supplies blood to the brain

**anterior tibial artery**: branches from the popliteal artery; supplies blood to the anterior tibial region; becomes the dorsalis pedis artery

**anterior tibial vein**: forms from the dorsal venous arch; drains the area near the tibialis anterior muscle and leads to the popliteal vein

**aorta**: largest artery in the body, originating from the left ventricle and descending to the abdominal region where it bifurcates into the common iliac arteries at the level of the fourth lumbar vertebra; arteries originating from the aorta distribute blood to virtually all tissues of the body

**aortic arch**: arc that connects the ascending aorta to the descending aorta; ends at the intervertebral disk between the fourth and fifth thoracic vertebrae
**aortic hiatus**: opening in the diaphragm that allows passage of the thoracic aorta into the abdominal region where it becomes the abdominal aorta

**arterial circle**: (also, circle of Willis) anastomosis located at the base of the brain that ensures continual blood supply; formed from branches of the internal carotid and vertebral arteries; supplies blood to the brain

**ascending aorta**: initial portion of the aorta, rising from the left ventricle for a distance of approximately 5 cm

**axillary artery**: continuation of the subclavian artery as it penetrates the body wall and enters the axillary region; supplies blood to the region near the head of the humerus (humeral circumflex arteries); the majority of the vessel continues into the brachium and becomes the brachial artery

**axillary vein**: major vein in the axillary region; drains the upper limb and becomes the subclavian vein

**azygos vein**: originates in the lumbar region and passes through the diaphragm into the thoracic cavity on the right side of the vertebral column; drains blood from the intercostal veins, esophageal veins, bronchial veins, and other veins draining the mediastinal region; leads to the superior vena cava

**basilar artery**: formed from the fusion of the two vertebral arteries; sends branches to the cerebellum, brain stem, and the posterior cerebral arteries; the main blood supply to the brain stem

**basilic vein**: superficial vein of the arm that arises from the palmar venous arches, intersects with the median cubital vein, parallels the ulnar vein, and continues into the upper arm; along with the brachial vein, it leads to the axillary vein

**brachial artery**: continuation of the axillary artery in the brachium; supplies blood to much of the brachial region; gives off several smaller branches that provide blood to the posterior surface of the arm in the region of the elbow; bifurcates into the radial and ulnar arteries at the coronoid fossa

**brachial vein**: deeper vein of the arm that forms from the radial and ulnar veins in the lower arm; leads to the axillary vein

**brachiocephalic artery**: single vessel located on the right side of the body; the first vessel branching from the aortic arch; gives rise to the right subclavian artery and the right common carotid artery; supplies blood to the head, neck, upper limb, and wall of the thoracic region

**brachiocephalic vein**: one of a pair of veins that form from a fusion of the external and internal jugular veins and the subclavian vein; subclavian, external and internal jugulars, vertebral, and internal thoracic veins lead to it; drains the upper thoracic region and flows into the superior vena cava

**bronchial artery**: systemic branch from the aorta that provides oxygenated blood to the lungs in addition to the pulmonary circuit

**bronchial vein**: drains the systemic circulation from the lungs and leads to the azygos vein

**cavernous sinus**: enlarged vein that receives blood from most of the other cerebral veins and the eye socket, and leads to the petrosal sinus

**celiac trunk**: (also, celiac artery) major branch of the abdominal aorta; gives rise to the left gastric artery, the splenic artery, and the common hepatic artery that forms the hepatic artery to the liver, the right gastric artery to the stomach, and the cystic artery to the gall bladder

**cephalic vein**: superficial vessel in the upper arm; leads to the axillary vein

**cerebrovascular accident (CVA)**: blockage of blood flow to the brain; also called a stroke

**circle of Willis**: (also, arterial circle) anastomosis located at the base of the brain that ensures continual blood supply; formed from branches of the internal carotid and vertebral arteries; supplies blood to the brain

**common carotid artery**: right common carotid artery arises from the brachiocephalic artery, and the left common carotid arises from the aortic arch; gives rise to the external and internal carotid arteries; supplies the respective sides of the head and neck

**common hepatic artery**: branch of the celiac trunk that forms the hepatic artery, the right gastric artery, and
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the cystic artery

**common iliac artery**: branch of the aorta that leads to the internal and external iliac arteries

**common iliac vein**: one of a pair of veins that flows into the inferior vena cava at the level of L5; the left common iliac vein drains the sacral region; divides into external and internal iliac veins near the inferior portion of the sacroiliac joint

**cystic artery**: branch of the common hepatic artery; supplies blood to the gall bladder

**deep femoral artery**: branch of the femoral artery; gives rise to the lateral circumflex arteries

**deep femoral vein**: drains blood from the deeper portions of the thigh and leads to the femoral vein

**descending aorta**: portion of the aorta that continues downward past the end of the aortic arch; subdivided into the thoracic aorta and the abdominal aorta

**digital arteries**: formed from the superficial and deep palmar arches; supply blood to the digits

**digital veins**: drain the digits and feed into the palmar arches of the hand and dorsal venous arch of the foot

**dorsal arch**: (also, arcuate arch) formed from the anastomosis of the dorsalis pedis artery and medial and plantar arteries; branches supply the distal portions of the foot and digits

**dorsal venous arch**: drains blood from digital veins and vessels on the superior surface of the foot

**dorsalis pedis artery**: forms from the anterior tibial artery; branches repeatedly to supply blood to the tarsal and dorsal regions of the foot

**esophageal artery**: branch of the thoracic aorta; supplies blood to the esophagus

**esophageal vein**: drains the inferior portions of the esophagus and leads to the azygos vein

**external carotid artery**: arises from the common carotid artery; supplies blood to numerous structures within the face, lower jaw, neck, esophagus, and larynx

**external iliac artery**: branch of the common iliac artery that leaves the body cavity and becomes a femoral artery; supplies blood to the lower limbs

**external iliac vein**: formed when the femoral vein passes into the body cavity; drains the legs and leads to the common iliac vein

**external jugular vein**: one of a pair of major veins located in the superficial neck region that drains blood from the more superficial portions of the head, scalp, and cranial regions, and leads to the subclavian vein

**femoral artery**: continuation of the external iliac artery after it passes through the body cavity; divides into several smaller branches, the lateral deep femoral artery, and the genicular artery; becomes the popliteal artery as it passes posterior to the knee

**femoral circumflex vein**: forms a loop around the femur just inferior to the trochanters; drains blood from the areas around the head and neck of the femur; leads to the femoral vein

**femoral vein**: drains the upper leg; receives blood from the great saphenous vein, the deep femoral vein, and the femoral circumflex vein; becomes the external iliac vein when it crosses the body wall

**fibular vein**: drains the muscles and integument near the fibula and leads to the popliteal vein

**genicular artery**: branch of the femoral artery; supplies blood to the region of the knee

**gonadal artery**: branch of the abdominal aorta; supplies blood to the gonads or reproductive organs; also described as ovarian arteries or testicular arteries, depending upon the sex of the individual

**gonadal vein**: generic term for a vein draining a reproductive organ; may be either an ovarian vein or a testicular vein, depending on the sex of the individual
**great cerebral vein:** receives most of the smaller vessels from the inferior cerebral veins and leads to the straight sinus

**great saphenous vein:** prominent surface vessel located on the medial surface of the leg and thigh; drains the superficial portions of these areas and leads to the femoral vein

**hemiazygos vein:** smaller vein complementary to the azygos vein; drains the esophageal veins from the esophagus and the left intercostal veins, and leads to the brachiocephalic vein via the superior intercostal vein

**hepatic artery proper:** branch of the common hepatic artery; supplies systemic blood to the liver

**hepatic portal system:** specialized circulatory pathway that carries blood from digestive organs to the liver for processing before being sent to the systemic circulation

**hepatic vein:** drains systemic blood from the liver and flows into the inferior vena cava

**inferior mesenteric artery:** branch of the abdominal aorta; supplies blood to the distal segment of the large intestine and rectum

**inferior phrenic artery:** branch of the abdominal aorta; supplies blood to the inferior surface of the diaphragm

**inferior vena cava:** large systemic vein that drains blood from areas largely inferior to the diaphragm; empties into the right atrium

**intercostal artery:** branch of the thoracic aorta; supplies blood to the muscles of the thoracic cavity and vertebral column

**intercostal vein:** drains the muscles of the thoracic wall and leads to the azygos vein

**internal carotid artery:** arises from the common carotid artery and begins with the carotid sinus; goes through the carotid canal of the temporal bone to the base of the brain; combines with branches of the vertebral artery forming the arterial circle; supplies blood to the brain

**internal iliac artery:** branch from the common iliac arteries; supplies blood to the urinary bladder, walls of the pelvis, external genitalia, and the medial portion of the femoral region; in females, also provide blood to the uterus and vagina

**internal iliac vein:** drains the pelvic organs and integument; formed from several smaller veins in the region; leads to the common iliac vein

**internal jugular vein:** one of a pair of major veins located in the neck region that passes through the jugular foramen and canal, flows parallel to the common carotid artery that is more or less its counterpart; primarily drains blood from the brain, receives the superficial facial vein, and empties into the subclavian vein

**internal thoracic artery:** (also, mammary artery) arises from the subclavian artery; supplies blood to the thymus, pericardium of the heart, and the anterior chest wall

**internal thoracic vein:** (also, internal mammary vein) drains the anterior surface of the chest wall and leads to the brachiocephalic vein

**lateral circumflex artery:** branch of the deep femoral artery; supplies blood to the deep muscles of the thigh and the ventral and lateral regions of the integument

**lateral plantar artery:** arises from the bifurcation of the posterior tibial arteries; supplies blood to the lateral plantar surfaces of the foot

**left gastric artery:** branch of the celiac trunk; supplies blood to the stomach

**lumbar arteries:** branches of the abdominal aorta; supply blood to the lumbar region, the abdominal wall, and spinal cord

**lumbar veins:** drain the lumbar portion of the abdominal wall and spinal cord; the superior lumbar veins drain into the azygos vein on the right or the hemiazygos vein on the left; blood from these vessels is returned to the superior vena cava rather than the inferior vena cava
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maxillary vein: drains blood from the maxillary region and leads to the external jugular vein

medial plantar artery: arises from the bifurcation of the posterior tibial arteries; supplies blood to the medial plantar surfaces of the foot

median antebrachial vein: vein that parallels the ulnar vein but is more medial in location; intertwines with the palmar venous arches

median cubital vein: superficial vessel located in the antecubital region that links the cephalic vein to the basilic vein in the form of a v; a frequent site for a blood draw

median sacral artery: continuation of the aorta into the sacrum

mediastinal artery: branch of the thoracic aorta; supplies blood to the mediastinum

middle cerebral artery: another branch of the internal carotid artery; supplies blood to the temporal and parietal lobes of the cerebrum

middle sacral vein: drains the sacral region and leads to the left common iliac vein

occipital sinus: enlarged vein that drains the occipital region near the falx cerebelli and flows into the left and right transverse sinuses, and also into the vertebral veins

ophthalmic artery: branch of the internal carotid artery; supplies blood to the eyes

ovarian artery: branch of the abdominal aorta; supplies blood to the ovary, uterine (Fallopian) tube, and uterus

ovarian vein: drains the ovary; the right ovarian vein leads to the inferior vena cava and the left ovarian vein leads to the left renal vein

palmar arches: superficial and deep arches formed from anastomoses of the radial and ulnar arteries; supply blood to the hand and digital arteries

palmar venous arches: drain the hand and digits, and feed into the radial and ulnar veins

parietal branches: (also, somatic branches) group of arterial branches of the thoracic aorta; includes those that supply blood to the thoracic cavity, vertebral column, and the superior surface of the diaphragm

pericardial artery: branch of the thoracic aorta; supplies blood to the pericardium

petrosal sinus: enlarged vein that receives blood from the cavernous sinus and flows into the internal jugular vein

phrenic vein: drains the diaphragm; the right phrenic vein flows into the inferior vena cava and the left phrenic vein leads to the left renal vein

plantar arch: formed from the anastomosis of the dorsalis pedis artery and medial and plantar arteries; branches supply the distal portions of the foot and digits

plantar veins: drain the foot and lead to the plantar venous arch

plantar venous arch: formed from the plantar veins; leads to the anterior and posterior tibial veins through anastomoses

popliteal artery: continuation of the femoral artery posterior to the knee; branches into the anterior and posterior tibial arteries

popliteal vein: continuation of the femoral vein behind the knee; drains the region behind the knee and forms from the fusion of the fibular and anterior and posterior tibial veins

posterior cerebral artery: branch of the basilar artery that forms a portion of the posterior segment of the arterial circle; supplies blood to the posterior portion of the cerebrum and brain stem

posterior communicating artery: branch of the posterior cerebral artery that forms part of the posterior
portion of the arterial circle; supplies blood to the brain

**posterior tibial artery**: branch from the popliteal artery that gives rise to the fibular or peroneal artery; supplies blood to the posterior tibial region

**posterior tibial vein**: forms from the dorsal venous arch; drains the area near the posterior surface of the tibia and leads to the popliteal vein

**pulmonary artery**: one of two branches, left and right, that divides off from the pulmonary trunk and leads to smaller arterioles and eventually to the pulmonary capillaries

**pulmonary circuit**: system of blood vessels that provide gas exchange via a network of arteries, veins, and capillaries that run from the heart, through the body, and back to the lungs

**pulmonary trunk**: single large vessel exiting the right ventricle that divides to form the right and left pulmonary arteries

**pulmonary veins**: two sets of paired vessels, one pair on each side, that are formed from the small venules leading away from the pulmonary capillaries that flow into the left atrium

**radial artery**: formed at the bifurcation of the brachial artery; parallels the radius; gives off smaller branches until it reaches the carpal region where it fuses with the ulnar artery to form the superficial and deep palmar arches; supplies blood to the lower arm and carpal region

**radial vein**: parallels the radius and radial artery; arises from the palmar venous arches and leads to the brachial vein

**renal artery**: branch of the abdominal aorta; supplies each kidney

**renal vein**: largest vein entering the inferior vena cava; drains the kidneys and leads to the inferior vena cava

**right gastric artery**: branch of the common hepatic artery; supplies blood to the stomach

**sigmoid sinuses**: enlarged veins that receive blood from the transverse sinuses; flow through the jugular foramen and into the internal jugular vein

**small saphenous vein**: located on the lateral surface of the leg; drains blood from the superficial regions of the lower leg and foot, and leads to the popliteal vein

**splenic artery**: branch of the celiac trunk; supplies blood to the spleen

**straight sinus**: enlarged vein that drains blood from the brain; receives most of the blood from the great cerebral vein and flows into the left or right transverse sinus

**subclavian artery**: right subclavian arises from the brachiocephalic artery, whereas the left subclavian artery arises from the aortic arch; gives rise to the internal thoracic, vertebral, and thyrocervical arteries; supplies blood to the arms, chest, shoulders, back, and central nervous system

**subclavian vein**: located deep in the thoracic cavity; becomes the axillary vein as it enters the axillary region; drains the axillary and smaller local veins near the scapular region; leads to the brachiocephalic vein

**subscapular vein**: drains blood from the subscapular region and leads to the axillary vein

**superior mesenteric artery**: branch of the abdominal aorta; supplies blood to the small intestine (duodenum, jejunum, and ileum), the pancreas, and a majority of the large intestine

**superior phrenic artery**: branch of the thoracic aorta; supplies blood to the superior surface of the diaphragm

**superior sagittal sinus**: enlarged vein located midsagittally between the meningeal and periosteal layers of the dura mater within the falx cerebri; receives most of the blood drained from the superior surface of the cerebrum and leads to the inferior jugular vein and the vertebral vein

**superior vena cava**: large systemic vein; drains blood from most areas superior to the diaphragm; empties into the right atrium
temporal vein: drains blood from the temporal region and leads to the external jugular vein

testicular artery: branch of the abdominal aorta; will ultimately travel outside the body cavity to the testes and form one component of the spermatic cord

testicular vein: drains the testes and forms part of the spermatic cord; the right testicular vein empties directly into the inferior vena cava and the left testicular vein empties into the left renal vein

thoracic aorta: portion of the descending aorta superior to the aortic hiatus

thyrocervical artery: arises from the subclavian artery; supplies blood to the thyroid, the cervical region, the upper back, and shoulder

transient ischemic attack (TIA): temporary loss of neurological function caused by a brief interruption in blood flow; also known as a mini-stroke

transverse sinuses: pair of enlarged veins near the lambdoid suture that drain the occipital, sagittal, and straight sinuses, and leads to the sigmoid sinuses

trunk: large vessel that gives rise to smaller vessels

ulnar artery: formed at the bifurcation of the brachial artery; parallels the ulna; gives off smaller branches until it reaches the carpal region where it fuses with the radial artery to form the superficial and deep palmar arches; supplies blood to the lower arm and carpal region

ulnar vein: parallels the ulna and ulnar artery; arises from the palmar venous arches and leads to the brachial vein

vertebral artery: arises from the subclavian artery and passes through the vertebral foramen through the foramen magnum to the brain; joins with the internal carotid artery to form the arterial circle; supplies blood to the brain and spinal cord

vertebral vein: arises from the base of the brain and the cervical region of the spinal cord; passes through the intervertebral foramina in the cervical vertebrae; drains smaller veins from the cranium, spinal cord, and vertebrae, and leads to the brachiocephalic vein; counterpart of the vertebral artery

visceral branches: branches of the descending aorta that supply blood to the viscera

Glossary: Development of Blood Vessels and Fetal Circulation

angioblasts: stem cells that give rise to blood vessels

angiogenesis: development of new blood vessels from existing vessels

blood islands: masses of developing blood vessels and formed elements from mesodermal cells scattered throughout the embryonic disc

ductus arteriosus: shunt in the fetal pulmonary trunk that diverts oxygenated blood back to the aorta

ductus venosus: shunt that causes oxygenated blood to bypass the fetal liver on its way to the inferior vena cava

foramen ovale: shunt that directly connects the right and left atria and helps to divert oxygenated blood from the fetal pulmonary circuit

hemangioblasts: embryonic stem cells that appear in the mesoderm and give rise to both angioblasts and pluripotent stem cells

umbilical arteries: pair of vessels that runs within the umbilical cord and carries fetal blood low in oxygen and
high in waste to the placenta for exchange with maternal blood

**umbilical vein**: single vessel that originates in the placenta and runs within the umbilical cord, carrying oxygen- and nutrient-rich blood to the fetal heart

**vascular tubes**: rudimentary blood vessels in a developing fetus
Glossary Section 19

Glossary: Anatomy of Lymphatic and Immune Systems

**adaptive immune response**: relatively slow but very specific and effective immune response controlled by lymphocytes

**afferent lymphatic vessels**: lead into a lymph node

**antibody**: antigen-specific protein secreted by plasma cells; immunoglobulin

**antigen**: molecule recognized by the receptors of B and T lymphocytes

**barrier defenses**: antipathogen defenses deriving from a barrier that physically prevents pathogens from entering the body to establish an infection

**B cells**: lymphocytes that act by differentiating into an antibody-secreting plasma cell

**bone marrow**: tissue found inside bones; the site of all blood cell differentiation and maturation of B lymphocytes

**bronchus-associated lymphoid tissue (BALT)**: lymphoid nodule associated with the respiratory tract

**chyle**: lipid-rich lymph inside the lymphatic capillaries of the small intestine

**cisterna chyli**: bag-like vessel that forms the beginning of the thoracic duct

**efferent lymphatic vessels**: lead out of a lymph node

**germinal centers**: clusters of rapidly proliferating B cells found in secondary lymphoid tissues

**high endothelial venules**: vessels containing unique endothelial cells specialized to allow migration of lymphocytes from the blood to the lymph node

**immune system**: series of barriers, cells, and soluble mediators that combine to response to infections of the body with pathogenic organisms

**innate immune response**: rapid but relatively nonspecific immune response

**lymph**: fluid contained within the lymphatic system

**lymph node**: one of the bean-shaped organs found associated with the lymphatic vessels

**lymphatic capillaries**: smallest of the lymphatic vessels and the origin of lymph flow

**lymphatic system**: network of lymphatic vessels, lymph nodes, and ducts that carries lymph from the tissues and back to the bloodstream.

**lymphatic trunks**: large lymphatics that collect lymph from smaller lymphatic vessels and empties into the blood via lymphatic ducts

**lymphocytes**: white blood cells characterized by a large nucleus and small rim of cytoplasm
lymphoid nodules: unencapsulated patches of lymphoid tissue found throughout the body

mucosa-associated lymphoid tissue (MALT): lymphoid nodule associated with the mucosa

naïve lymphocyte: mature B or T cell that has not yet encountered antigen for the first time

natural killer cell (NK): cytotoxic lymphocyte of innate immune response

plasma cell: differentiated B cell that is actively secreting antibody

primary lymphoid organ: site where lymphocytes mature and proliferate; red bone marrow and thymus gland

right lymphatic duct: drains lymph fluid from the upper right side of body into the right subclavian vein

secondary lymphoid organs: sites where lymphocytes mount adaptive immune responses; examples include lymph nodes and spleen

spleen: secondary lymphoid organ that filters pathogens from the blood (white pulp) and removes degenerating or damaged blood cells (red pulp)

T cell: lymphocyte that acts by secreting molecules that regulate the immune system or by causing the destruction of foreign cells, viruses, and cancer cells

thoracic duct: large duct that drains lymph from the lower limbs, left thorax, left upper limb, and the left side of the head

thymocyte: immature T cell found in the thymus

thymus: primary lymphoid organ; where T lymphocytes proliferate and mature

tonsils: lymphoid nodules associated with the nasopharynx

Glossary: T Lymphocytes and their Functional Types

antigenic determinant: (also, epitope) one of the chemical groups recognized by a single type of lymphocyte antigen receptor

antigen presentation: binding of processed antigen to the protein-binding cleft of a major histocompatibility complex molecule

antigen processing: internalization and digestion of antigen in an antigen-presenting cell

antigen receptor: two-chain receptor by which lymphocytes recognize antigen

clone: group of lymphocytes sharing the same antigen receptor

clonal expansion: growth of a clone of selected lymphocytes

clonal selection: stimulating growth of lymphocytes that have specific receptors

constant region domain: part of a lymphocyte antigen receptor that does not vary much between different receptor types

cytotoxic T cells (Tc): T lymphocytes with the ability to induce apoptosis in target cells

effector T cells: immune cells with a direct, adverse effect on a pathogen

helper T cells (Th): T cells that secrete cytokines to enhance other immune responses, involved in activation of
Anatomy

both B and T cell lymphocytes

**immunological memory**: ability of the adaptive immune response to mount a stronger and faster immune response upon re-exposure to a pathogen

**major histocompatibility complex (MHC)**: gene cluster whose proteins present antigens to T cells

**memory T cells**: long-lived immune cell reserved for future exposure to an pathogen

**MHC class I**: found on most cells of the body, it binds to the CD8 molecule on T cells

**MHC class II**: found on macrophages, dendritic cells, and B cells, it binds to CD4 molecules on T cells

**negative selection**: selection against thymocytes in the thymus that react with self-antigen

**polyclonal response**: response by multiple clones to a complex antigen with many determinants

**primary adaptive response**: immune system’s response to the first exposure to a pathogen

**positive selection**: selection of thymocytes within the thymus that interact with self, but not non-self, MHC molecules

**regulatory T cells (Treg)**: (also, suppressor T cells) class of CD4 T cells that regulates other T cell responses

**secondary adaptive response**: immune response observed upon re-exposure to a pathogen, which is stronger and faster than a primary response

**T cell tolerance**: process during T cell differentiation where most T cells that recognize antigens from one’s own body are destroyed

**Th1 cells**: cells that secrete cytokines that enhance the activity of macrophages and other cells

**Th2 cells**: cells that secrete cytokines that induce B cells to differentiate into antibody-secreting plasma cells

**variable region domain**: part of a lymphocyte antigen receptor that varies considerably between different receptor types

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**Glossary: B Lymphocytes and Antibodies**

**active immunity**: immunity developed from an individual’s own immune system

**central tolerance**: B cell tolerance induced in immature B cells of the bone marrow

**class switching**: ability of B cells to change the class of antibody they produce without altering the specificity for antigen

**clonal anergy**: process whereby B cells that react to soluble antigens in bone marrow are made nonfunctional

**clonal deletion**: removal of self-reactive B cells by inducing apoptosis

**Fc region**: in an antibody molecule, the site where the two termini of the heavy chains come together; many cells have receptors for this portion of the antibody, adding functionality to these molecules

**heavy chain**: larger protein chain of an antibody

**IgA**: antibody whose dimer is secreted by exocrine glands, is especially effective against digestive and respiratory pathogens, and can pass immunity to an infant through breastfeeding

**IgD**: class of antibody whose only known function is as a receptor on naive B cells; important in B cell activation

**IgE**: antibody that binds to mast cells and causes antigen-specific degranulation during an allergic response
Anatomy

**IgG:** main blood antibody of late primary and early secondary responses; passed from mother to unborn child via placenta

**IgM:** antibody whose monomer is a surface receptor of naive B cells; the pentamer is the first antibody made blood plasma during primary responses

**Immunoglobulin:** protein antibody; occurs as one of five main classes

**Light chain:** small protein chain of an antibody

**Passive immunity:** transfer of immunity to a pathogen to an individual that lacks immunity to this pathogen usually by the injection of antibodies

**Peripheral tolerance:** mature B cell made tolerant by lack of T cell help

**T cell-dependent antigen:** antigen that binds to B cells, which requires signals from T cells to make antibody

**T cell-independent antigen:** binds to B cells, which do not require signals from T cells to make antibody

Glossary: Diseases Associated with Depressed or Overactive Immune Responses

**Delayed hypersensitivity:** (type IV) T cell-mediated immune response against pathogens infiltrating interstitial tissues, causing cellular infiltrate

**Immediate hypersensitivity:** (type I) IgE-mediated mast cell degranulation caused by crosslinking of surface IgE by antigen

**Sensitization:** first exposure to an antigen

**Severe combined immunodeficiency disease (SCID):** genetic mutation that affects both T cell and B cell arms of the immune response

**Type I hypersensitivity:** immediate response mediated by mast cell degranulation caused by the crosslinking of the antigen-specific IgE molecules on the mast cell surface

**Type II hypersensitivity:** cell damage caused by the binding of antibody and the activation of complement, usually against red blood cells

**Type III hypersensitivity:** damage to tissues caused by the deposition of antibody-antigen (immune) complexes followed by the activation of complement

Glossary: Transplant and Cancer Immunology

**Erythroblastosis fetalis:** disease of Rh factor-positive newborns in Rh-negative mothers with multiple Rh-positive children; resulting from the action of maternal antibodies against fetal blood

**Graft-versus-host disease:** in bone marrow transplants; occurs when the transplanted cells mount an immune response against the recipient

**MHC polygeny:** multiple MHC genes and their proteins found in body cells

**MHC polymorphism:** multiple alleles for each individual MHC locus

**Psychoneuroimmunology:** study of the connections between the immune, nervous, and endocrine systems
Anatomy

**tissue typing:** typing of MHC molecules between a recipient and donor for use in a potential transplantation procedure
Glossary Section 20

Glossary: Organs and Structures of the Respiratory System

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

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

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

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

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

**alveolar sac:** cluster of alveoli

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

**apex:** tip of the external nose

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

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

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

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

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

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

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

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

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

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

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

**glottis:** opening between the vocal folds through which air passes when producing speech
laryngeal prominence: region where the two lamina of the thyroid cartilage join, forming a protrusion known as “Adam’s apple”

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

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

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

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

naris: (plural = nares) opening of the nostrils

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

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

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

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

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

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

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

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

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

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

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

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

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

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

root: region of the external nose between the eyebrows

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

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

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

true vocal cord: one of the pair of folded, white membranes that have a free inner edge that oscillates as air passes through to produce sound
**type I alveolar cell:** squamous epithelial cells that are the major cell type in the alveolar wall; highly permeable to gases

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

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

**Glossary: The Lungs**

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

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

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

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

**lungs:** organ of the respiratory system that performs gas exchange

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

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

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

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

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

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

**Glossary: Embryonic Development of the Respiratory System**

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

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

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

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

**olfactory pit:** invaginated ectodermal tissue in the anterior portion of the head region of an embryo that will form the nasal cavity
Glossary Section 21

Glossary: Characteristics of Urine

**anuria**: absence of urine produced; production of 50 mL or less per day

**leukocyte esterase**: enzyme produced by leukocytes that can be detected in the urine and that serves as an indirect indicator of urinary tract infection

**oliguria**: below normal urine production of 400–500 mL/day

**polyuria**: urine production in excess of 2.5 L/day; may be caused by diabetes insipidus, diabetes mellitus, or excessive use of diuretics

**specific gravity**: weight of a liquid compared to pure water, which has a specific gravity of 1.0; any solute added to water will increase its specific gravity

**urinalysis**: analysis of urine to diagnose disease

**urochrome**: heme-derived pigment that imparts the typical yellow color of urine

Glossary: Gross Anatomy of Urine Transport

**anatomical sphincter**: smooth or skeletal muscle surrounding the lumen of a vessel or hollow organ that can restrict flow when contracted

**detrusor muscle**: smooth muscle in the bladder wall; fibers run in all directions to reduce the size of the organ when emptying it of urine

**external urinary sphincter**: skeletal muscle; must be relaxed consciously to void urine

**internal urinary sphincter**: smooth muscle at the juncture of the bladder and urethra; relaxes as the bladder fills to allow urine into the urethra

**incontinence**: loss of ability to control micturition

**micturition**: also called urination or voiding

**physiological sphincter**: sphincter consisting of circular smooth muscle indistinguishable from adjacent muscle but possessing differential innervations, permitting its function as a sphincter; structurally weak

**retroperitoneal**: outside the peritoneal cavity; in the case of the kidney and ureters, between the parietal peritoneum and the abdominal wall

**sacral micturition center**: group of neurons in the sacral region of the spinal cord that controls urination; acts reflexively unless its action is modified by higher brain centers to allow voluntary urination

**trigon**: area at the base of the bladder marked by the two ureters in the posterior-lateral aspect and the urethral orifice in the anterior aspect oriented like points on a triangle

**urethra**: transports urine from the bladder to the outside environment
Glossary: Gross Anatomy of the Kidney

**Bowman’s capsule:** cup-shaped sack lined by a simple squamous epithelium (parietal surface) and specialized cells called podocytes (visceral surface) that participate in the filtration process; receives the filtrate which then passes on to the PCTs

**calyces:** cup-like structures receiving urine from the collecting ducts where it passes on to the renal pelvis and ureter

**cortical nephrons:** nephrons with loops of Henle that do not extend into the renal medulla

**distal convoluted tubules:** portions of the nephron distal to the loop of Henle that receive hyposmotic filtrate from the loop of Henle and empty into collecting ducts

**efferent arteriole:** arteriole carrying blood from the glomerulus to the capillary beds around the convoluted tubules and loop of Henle; portion of the portal system

**glomerulus:** tuft of capillaries surrounded by Bowman’s capsule; filters the blood based on size

**juxtamedullary nephrons:** nephrons adjacent to the border of the cortex and medulla with loops of Henle that extend into the renal medulla

**loop of Henle:** descending and ascending portions between the proximal and distal convoluted tubules; those of cortical nephrons do not extend into the medulla, whereas those of juxtamedullary nephrons do extend into the medulla

**nephrons:** functional units of the kidney that carry out all filtration and modification to produce urine; consist of renal corpuscles, proximal and distal convoluted tubules, and descending and ascending loops of Henle; drain into collecting ducts

**medulla:** inner region of kidney containing the renal pyramids

**peritubular capillaries:** second capillary bed of the renal portal system; surround the proximal and distal convoluted tubules; associated with the vasa recta

**proximal convoluted tubules (PCTs):** tortuous tubules receiving filtrate from Bowman’s capsule; most active part of the nephron in reabsorption and secretion

**renal columns:** extensions of the renal cortex into the renal medulla; separates the renal pyramids; contains blood vessels and connective tissues

**renal corpuscle:** consists of the glomerulus and Bowman’s capsule

**renal cortex:** outer part of kidney containing all of the nephrons; some nephrons have loops of Henle extending into the medulla

**renal fat pad:** adipose tissue between the renal fascia and the renal capsule that provides protective cushioning to the kidney

**renal hilum:** recessed medial area of the kidney through which the renal artery, renal vein, ureters, lymphatics, and nerves pass

**renal papillae:** medullary area of the renal pyramids where collecting ducts empty urine into the minor calyces

**renal pyramids:** six to eight cone-shaped tissues in the medulla of the kidney containing collecting ducts and the loops of Henle of juxtamedullary nephrons

**vasa recta:** branches of the efferent arterioles that parallel the course of the loops of Henle and are continuous with the peritubular capillaries; with the glomerulus, form a portal system
**Glossary: Microscopic Anatomy of the Kidney**

**angiotensin-converting enzyme (ACE):** enzyme produced by the lungs that catalyzes the reaction of inactive angiotensin I into active angiotensin II

**angiotensin I:** protein produced by the enzymatic action of renin on angiotensinogen; inactive precursor of angiotensin II

**angiotensin II:** protein produced by the enzymatic action of ACE on inactive angiotensin I; actively causes vasoconstriction and stimulates aldosterone release by the adrenal cortex

**angiotensinogen:** inactive protein in the circulation produced by the liver; precursor of angiotensin I; must be modified by the enzymes renin and ACE to be activated

**aquaporin:** protein-forming water channels through the lipid bilayer of the cell; allows water to cross; activation in the collecting ducts is under the control of ADH

**brush border:** formed by microvilli on the surface of certain cuboidal cells; in the kidney it is found in the PCT; increases surface area for absorption in the kidney

**fenestrations:** small windows through a cell, allowing rapid filtration based on size; formed in such a way as to allow substances to cross through a cell without mixing with cell contents

**filtration slits:** formed by pedicels of podocytes; substances filter between the pedicels based on size

**forming urine:** filtrate undergoing modifications through secretion and reabsorption before true urine is produced

**juxtaglomerular apparatus (JGA):** located at the juncture of the DCT and the afferent and efferent arterioles of the glomerulus; plays a role in the regulation of renal blood flow and GFR

**juxtaglomerular cell:** modified smooth muscle cells of the afferent arteriole; secretes renin in response to a drop in blood pressure

**macula densa:** cells found in the part of the DCT forming the JGA; sense Na⁺ concentration in the forming urine

**mesangial:** contractile cells found in the glomerulus; can contract or relax to regulate filtration rate

**pedicels:** finger-like projections of podocytes surrounding glomerular capillaries; interdigitate to form a filtration membrane

**podocytes:** cells forming finger-like processes; form the visceral layer of Bowman’s capsule; pedicels of the podocytes interdigitate to form a filtration membrane

**renin:** enzyme produced by juxtaglomerular cells in response to decreased blood pressure or sympathetic nervous activity; catalyzes the conversion of angiotensinogen into angiotensin I
Glossary Section 22

Glossary: Overview of the Digestive System

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

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

**motility**: movement of food through the GI tract

**mucosa**: innermost lining of the alimentary canal

**muscularis**: muscle (skeletal or smooth) layer of the alimentary canal wall

**myenteric plexus**: (plexus of Auerbach) major nerve supply to alimentary canal wall; controls motility

**retroperitoneal**: located posterior to the peritoneum

**serosa**: outermost layer of the alimentary canal wall present in regions within the abdominal cavity

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

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

Glossary: Digestive System Processes and Regulation

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

**chemical digestion**: enzymatic breakdown of food

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

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

**ingestion**: taking food into the GI tract through the mouth

**mastication**: chewing

**mechanical digestion**: chewing, mixing, and segmentation that prepares food for chemical digestion

**peristalsis**: muscular contractions and relaxations that propel food through the GI tract

**propulsion**: voluntary process of swallowing and the involuntary process of peristalsis that moves food through the digestive tract

**segmentation**: alternating contractions and relaxations of non-adjacent segments of the intestine that move food forward and backward, breaking it apart and mixing it with digestive juices
Glossary: The Mouth, Pharynx, and Esophagus

bolus: mass of chewed food

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

crown: portion of tooth visible superior to the gum line

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

deciduous tooth: one of 20 “baby teeth”

deglutition: three-stage process of swallowing

dens: tooth

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

dentition: set of teeth

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

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

fauces: opening between the oral cavity and the oropharynx

ingiva: gum

incisor: midline, chisel-shaped tooth used for cutting into food

labium: lip

labial frenulum: midline mucous membrane fold that attaches the inner surface of the lips to the gums

laryngopharynx: part of the pharynx that functions in respiration and digestion

lingual frenulum: mucous membrane fold that attaches the bottom of the tongue to the floor of the mouth

lingual lipase: digestive enzyme from glands in the tongue that acts on triglycerides

lower esophageal sphincter: smooth muscle sphincter that regulates food movement from the esophagus to the stomach

molar: tooth used for crushing and grinding food

oral cavity: (also, buccal cavity) mouth

oral vestibule: part of the mouth bounded externally by the cheeks and lips, and internally by the gums and teeth

oropharynx: part of the pharynx continuous with the oral cavity that functions in respiration and digestion

palatoglossal arch: muscular fold that extends from the lateral side of the soft palate to the base of the tongue

palatopharyngeal arch: muscular fold that extends from the lateral side of the soft palate to the side of the pharynx

parotid gland: one of a pair of major salivary glands located inferior and anterior to the ears

permanent tooth: one of 32 adult teeth

pharynx: throat
premolar: (also, bicuspid) transitional tooth used for mastication, crushing, and grinding food

pulp cavity: deepest portion of a tooth, containing nerve endings and blood vessels

root: portion of a tooth embedded in the alveolar processes beneath the gum line

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

salivary amylase: digestive enzyme in saliva that acts on starch

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

salivation: secretion of saliva

soft palate: posterior region of the bottom portion of the nasal cavity that consists of skeletal muscle

sublingual gland: one of a pair of major salivary glands located beneath the tongue

submandibular gland: one of a pair of major salivary glands located in the floor of the mouth

tongue: accessory digestive organ of the mouth, the bulk of which is composed of skeletal muscle

upper esophageal sphincter: skeletal muscle sphincter that regulates food movement from the pharynx to the esophagus

voluntary phase: initial phase of deglutition, in which the bolus moves from the mouth to the oropharynx

Glossary: The Stomach

body: mid-portion of the stomach

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

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

chief cell: gastric gland cell that secretes pepsinogen

enteroendocrine cell: gastric gland cell that releases hormones

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

G cell: gastrin-secreting enteroendocrine cell

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

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

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

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

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

hydrochloric acid (HCl): digestive acid secreted by parietal cells in the stomach

intrinsic factor: glycoprotein required for vitamin B_{12} absorption in the small intestine

intestinal phase: phase of gastric secretion that begins when chyme enters the intestine

mixing wave: unique type of peristalsis that occurs in the stomach

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

mucous neck cell: gastric gland cell that secretes a uniquely acidic mucus

parietal cell: gastric gland cell that secretes hydrochloric acid and intrinsic factor

pepsinogen: inactive form of pepsin

pyloric antrum: wider, more superior part of the pylorus

pyloric canal: narrow, more inferior part of the pylorus

pyloric sphincter: sphincter that controls stomach emptying

pylorus: lower, funnel-shaped part of the stomach that is continuous with the duodenum

rugula: fold of alimentary canal mucosa and submucosa in the empty stomach and other organs

stomach: alimentary canal organ that contributes to chemical and mechanical digestion of food from the esophagus before releasing it, as chyme, to the small intestine

Glossary: The Small and Large Intestines

anal canal: final segment of the large intestine

anal column: long fold of mucosa in the anal canal

anal sinus between anal columns

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

ascending colon: first region of the colon

bacterial flora: bacteria in the large intestine

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

cecum: pouch forming the beginning of the large intestine

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

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

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

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

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

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

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

feces: semisolid waste product of digestion

flatus: gas in the intestine

gastrocolic reflex: propulsive movement in the colon activated by the presence of food in the stomach

gastroileal reflex: long reflex that increases the strength of segmentation in the ileum

hastrum: small pouch in the colon created by tonic contractions of teniae coli

haustral contraction: slow segmentation in the large intestine
**hepatopancreatic ampulla**: (also, ampulla of Vater) bulb-like point in the wall of the duodenum where the bile duct and main pancreatic duct unite

**hepatopancreatic sphincter**: (also, sphincter of Oddi) sphincter regulating the flow of bile and pancreatic juice into the duodenum

**ileocecal sphincter**: sphincter located where the small intestine joins with the large intestine

**ileum**: end of the small intestine between the jejunum and the large intestine

**internal anal sphincter**: involuntary smooth muscle sphincter in the anal canal

**intestinal gland**: (also, crypt of Lieberkühn) gland in the small intestinal mucosa that secretes intestinal juice

**intestinal juice**: mixture of water and mucus that helps absorb nutrients from chyme

**jejunum**: middle part of the small intestine between the duodenum and the ileum

**lacteal**: lymphatic capillary in the villi

**large intestine**: terminal portion of the alimentary canal

**left colic flexure**: (also, splenic flexure) point where the transverse colon curves below the inferior end of the spleen

**main pancreatic duct**: (also, duct of Wirsung) duct through which pancreatic juice drains from the pancreas

**major duodenal papilla**: point at which the hepatopancreatic ampulla opens into the duodenum

**mass movement**: long, slow, peristaltic wave in the large intestine

**mesoappendix**: mesentery of the appendix

**microvillus**: small projection of the plasma membrane of the absorptive cells of the small intestinal mucosa

**migrating motility complex**: form of peristalsis in the small intestine

**motilin**: hormone that initiates migrating motility complexes

**pectinate line**: horizontal line that runs like a ring, perpendicular to the inferior margins of the anal sinuses

**rectal valve**: one of three transverse folds in the rectum where feces is separated from flatus

**rectum**: part of the large intestine between the sigmoid colon and anal canal

**right colic flexure**: (also, hepatic flexure) point, at the inferior surface of the liver, where the ascending colon turns abruptly to the left

**saccharolytic fermentation**: anaerobic decomposition of carbohydrates

**sigmoid colon**: end portion of the colon, which terminates at the rectum

**small intestine**: section of the alimentary canal where most digestion and absorption occurs

**tenia coli**: one of three smooth muscle bands that make up the longitudinal muscle layer of the muscularis in all of the large intestine except the terminal end

**transverse colon**: part of the colon between the ascending colon and the descending colon

**Valsalva’s maneuver**: voluntary contraction of the diaphragm and abdominal wall muscles and closing of the glottis, which increases intra-abdominal pressure and facilitates defecation

**villus**: projection of the mucosa of the small intestine
Glossary: Accessory Organs in Digestion: The Liver, Pancreas, and Gallbladder

accessory duct: (also, duct of Santorini) duct that runs from the pancreas into the duodenum  
acinus: cluster of glandular epithelial cells in the pancreas that secretes pancreatic juice in the pancreas  
bile: alkaline solution produced by the liver and important for the emulsification of lipids  
bile canaliculus: small duct between hepatocytes that collects bile  
bilirubin: main bile pigment, which is responsible for the brown color of feces  
central vein: vein that receives blood from hepatic sinusoids  
common bile duct: structure formed by the union of the common hepatic duct and the gallbladder’s cystic duct  
common hepatic duct: duct formed by the merger of the two hepatic ducts  
cystic duct: duct through which bile drains and enters the gallbladder  
enterohepatic circulation: recycling mechanism that conserves bile salts  
enteropeptidase: intestinal brush-border enzyme that activates trypsinogen to trypsin  
gallbladder: accessory digestive organ that stores and concentrates bile  
hepatic artery: artery that supplies oxygenated blood to the liver  
hepatic lobule: hexagonal-shaped structure composed of hepatocytes that radiate outward from a central vein  
hepatic portal vein: vein that supplies deoxygenated nutrient-rich blood to the liver  
hepatic sinusoid: blood capillaries between rows of hepatocytes that receive blood from the hepatic portal vein and the branches of the hepatic artery  
hepatic vein: vein that drains into the inferior vena cava  
hepatocytes: major functional cells of the liver  
liver: largest gland in the body whose main digestive function is the production of bile  
pancreas: accessory digestive organ that secretes pancreatic juice  
pancreatic juice: secretion of the pancreas containing digestive enzymes and bicarbonate  
porta hepatis: “gateway to the liver” where the hepatic artery and hepatic portal vein enter the liver  
portal triad: bile duct, hepatic artery branch, and hepatic portal vein branch  
reticuloendothelial cell: (also, Kupffer cell) phagocyte in hepatic sinusoids that filters out material from venous blood from the alimentary canal
Glossary Section 23

Glossary: Development of the Reproductive System

Müllerian duct: duct system present in the embryo that will eventually form the EPC structures

puberty: life stage during which the EPC or SPC organs becomes anatomically and physiologically mature

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

Wolffian duct: duct system present in the embryo that will eventually form the internal SPC structures

Glossary: Anatomy of the Sperm Producing and Conducting Organs

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

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

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

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

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

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

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

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

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

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

gonads: reproductive organs (testes in those with SPC organs, ovaries in those with EPC organs) that produce gametes and reproductive hormones
Anatomy

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

Interstitial cells: cells between the seminiferous tubules of the testes that produce testosterone

penis: organ of copulation in those with SPC organs

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

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

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

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

semenal vesicle: gland that produces seminal fluid, which contributes to semen

seminiferous tubules: tube structures within the testes where spermatogenesis occurs

sperm: (also, spermatozoon) male gamete

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

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

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

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

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

spermiogenesis: transformation of spermatids to spermatozoa during spermatogenesis

Sustentacular cells: cells that support germ cells through the process of spermatogenesis

testes: (singular = testis) sperm producing organs

Glossary: Anatomy of the Egg Producing and Conducting Organs

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

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

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

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

body of uterus: middle section of the uterus

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

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

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

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

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

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

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

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

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

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

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

**greater vestibular glands:** glands that produce a thick mucus that maintains moisture in the vulva area; also referred to as Bartholin’s glands

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

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

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

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

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

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

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

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

**menarche:** first menstruation in a pubertal individual

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

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

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

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

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

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

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

**oogonia:** ovarian stem cells that undergo mitosis during fetal development of those with EPC organs to form primary oocytes

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

phase

ovaries: gonads of those with EPC organs that produce oocytes and sex steroid hormones (notably estrogen and progesterone)

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

ovum: haploid gamete of those with EPC organs resulting from completion of meiosis II at fertilization

perimetrium: outer epithelial layer of uterine wall

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

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

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

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

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

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

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

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

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

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

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

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

vagina: tunnel-like organ that provides access to the uterus for the deposition of semen, and from the uterus for the birth of a baby

vulva: external genitalia of those with EPC organs
Glossary Section 24

Glossary: Fertilization

**acrosome**: cap-like vesicle located at the anterior-most region of a sperm that is rich with lysosomal enzymes capable of digesting the protective layers surrounding the oocyte

**acrosomal reaction**: release of digestive enzymes by sperm that enables them to burrow through the corona radiata and penetrate the zona pellucida of an oocyte prior to fertilization

**capacitation**: process that occurs in the female reproductive tract in which sperm are prepared for fertilization; leads to increased motility and changes in their outer membrane that improve their ability to release enzymes capable of digesting an oocyte’s outer layers

**corona radiata**: in an oocyte, a layer of granulosa cells that surrounds the oocyte and that must be penetrated by sperm before fertilization can occur

**cortical reaction**: following fertilization, the release of cortical granules from the oocyte’s plasma membrane into the zona pellucida creating a fertilization membrane that prevents any further attachment or penetration of sperm; part of the slow block to polyspermy

**fertilization**: unification of genetic material from the haploid gametes of EPC and SPC organs

**fertilization membrane**: impenetrable barrier that coats a nascent zygote; part of the slow block to polyspermy

**polyspermy**: penetration of an oocyte by more than one sperm

**zona pellucida**: thick, gel-like glycoprotein membrane that coats the oocyte and must be penetrated by sperm before fertilization can occur

**zygote**: a diploid cell resulting from the fertilization of haploid gametes from EPC and SPC organs

Glossary: Embryonic Development

**allantois**: finger-like outpocketing of yolk sac forms the primitive excretory duct of the embryo; precursor to the urinary bladder

**amnion**: transparent membranous sac that encloses the developing fetus and fills with amniotic fluid

**amniotic cavity**: cavity that opens up between the inner cell mass and the trophoblast; develops into amnion

**blastocoel**: fluid-filled cavity of the blastocyst

**blastocyst**: term for the conceptus at the developmental stage that consists of about 100 cells shaped into an inner cell mass that is fated to become the embryo and an outer trophoblast that is fated to become the associated fetal membranes and placenta

**blastomere**: daughter cell of a cleavage

**chorion**: membrane that develops from the syncytiotrophoblast, cytotrophoblast, and mesoderm; surrounds the embryo and forms the fetal portion of the placenta through the chorionic villi
Anatomy

**chorionic membrane:** precursor to the chorion; forms from extra-embryonic mesoderm cells

**chorionic villi:** projections of the chorionic membrane that burrow into the endometrium and develop into the placenta

**cleavage:** form of mitotic cell division in which the cell divides but the total volume remains unchanged; this process serves to produce smaller and smaller cells

**conceptus:** pre-implantation stage of a fertilized egg and its associated membranes

**ectoderm:** primary germ layer that develops into the central and peripheral nervous systems, sensory organs, epidermis, hair, and nails

**ectopic pregnancy:** implantation of an embryo outside of the uterus

**embryo:** developing human during weeks 3–8

**embryonic folding:** process by which an embryo develops from a flat disc of cells to a three-dimensional shape resembling a cylinder

**endoderm:** primary germ layer that goes on to form the gastrointestinal tract, liver, pancreas, and lungs

**epiblast:** upper layer of cells of the embryonic disc that forms from the inner cell mass; gives rise to all three germ layers

**fetus:** developing human during the time from the end of the embryonic period (week 9) to birth

**gastrulation:** process of cell migration and differentiation into three primary germ layers following cleavage and implantation

**gestation:** in human development, the period required for embryonic and fetal development in utero; pregnancy

**human chorionic gonadotropin (hCG):** hormone that directs the corpus luteum to survive, enlarge, and continue producing progesterone and estrogen to suppress menses and secure an environment suitable for the developing embryo

**hypoblast:** lower layer of cells of the embryonic disc that extend into the blastocoel to form the yolk sac

**implantation:** process by which a blastocyst embeds itself in the uterine endometrium

**inner cell mass:** cluster of cells within the blastocyst that is fated to become the embryo

**mesoderm:** primary germ layer that becomes the skeleton, muscles, connective tissue, heart, blood vessels, and kidneys

**morula:** tightly packed sphere of blastomeres that has reached the uterus but has not yet implanted itself

**neural plate:** thickened layer of neuroepithelium that runs longitudinally along the dorsal surface of an embryo and gives rise to nervous system tissue

**neural fold:** elevated edge of the neural groove

**neural tube:** precursor to structures of the central nervous system, formed by the invagination and separation of neuroepithelium

**neurulation:** embryonic process that establishes the central nervous system

**notochord:** rod-shaped, mesoderm-derived structure that provides support for growing fetus

**organogenesis:** development of the rudimentary structures of all of an embryo’s organs from the germ layers

**placenta:** organ that forms during pregnancy to nourish the developing fetus; also regulates waste and gas exchange between parent and fetus
placenta previa: low placement of fetus within uterus causes placenta to partially or completely cover the opening of the cervix as it grows

placentation: formation of the placenta; complete by weeks 14–16 of pregnancy

primitive streak: indentation along the dorsal surface of the epiblast through which cells migrate to form the endoderm and mesoderm during gastrulation

somite: one of the paired, repeating blocks of tissue located on either side of the notochord in the early embryo

syncytiotrophoblast: superficial cells of the trophoblast that fuse to form a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall

trophoblast: fluid-filled shell of squamous cells destined to become the chorionic villi, placenta, and associated fetal membranes

umbilical cord: connection between the developing conceptus and the placenta; carries deoxygenated blood and wastes from the fetus and returns nutrients and oxygen from the parent

yolk sac: membrane associated with primitive circulation to the developing embryo; source of the first blood cells and germ cells and contributes to the umbilical cord structure

Glossary: Fetal Development

ductus arteriosus: shunt in the pulmonary trunk that diverts oxygenated blood back to the aorta

ductus venosus: shunt that causes oxygenated blood to bypass the fetal liver on its way to the inferior vena cava

foramen ovale: shunt that directly connects the right and left atria and helps divert oxygenated blood from the fetal pulmonary circuit

lanugo: silk-like hairs that coat the fetus; shed later in fetal development

meconium: fetal wastes consisting of ingested amniotic fluid, cellular debris, mucus, and bile

quickening: fetal movements that are strong enough to be felt by the mother

shunt: circulatory shortcut that diverts the flow of blood from one region to another

vernix caseosa: waxy, cheese-like substance that protects the delicate fetal skin until birth

Glossary: Gestational Parent Changes During Pregnancy, Labor, and Birth

afterbirth: third stage of childbirth in which the placenta and associated fetal membranes are expelled

Braxton Hicks contractions: weak and irregular peristaltic contractions that can occur in the second and third trimesters; they do not indicate that childbirth is imminent

dilation: first stage of childbirth, involving an increase in cervical diameter

episiotomy: incision made in the posterior vaginal wall and perineum that facilitates vaginal birth

expulsion: second stage of childbirth, during which the parent bears down with contractions; this stage ends in birth
**Anatomy**

**involution**: postpartum shrinkage of the uterus back to its pre-pregnancy volume

**lightening**: descent of the fetus lower into the pelvis in late pregnancy; also called “dropping”

**lochia**: postpartum vaginal discharge that begins as blood and ends as a whitish discharge; the end of lochia signals that the site of placental attachment has healed

**parturition**: childbirth

**trimester**: division of the duration of a pregnancy into three 3-month terms

**true labor**: regular contractions that immediately precede childbirth; they do not abate with hydration or rest, and they become more frequent and powerful with time

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**Glossary: Adjustments of the Infant at Birth and Postnatal Stages**

**brown adipose tissue**: highly vascularized fat tissue that is packed with mitochondria; these properties confer the ability to oxidize fatty acids to generate heat

**nonshivering thermogenesis**: process of breaking down brown adipose tissue to produce heat in the absence of a shivering response

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**Glossary: Lactation**

**colostrum**: thick, yellowish substance secreted from a mother’s breasts in the first postpartum days; rich in immunoglobulins

**foremilk**: watery, translucent breast milk that is secreted first during a feeding and is rich in lactose and protein; quenches the infant’s thirst

**hindmilk**: opaque, creamy breast milk delivered toward the end of a feeding; rich in fat; satisfies the infant’s appetite

**lactation**: process by which milk is synthesized and secreted from the mammary glands of the postpartum breast in response to sucking at the nipple

**let-down reflex**: release of milk from the alveoli triggered by infant sucking

**prolactin**: pituitary hormone that establishes and maintains the supply of breast milk; also important for the mobilization of maternal micronutrients for breast milk