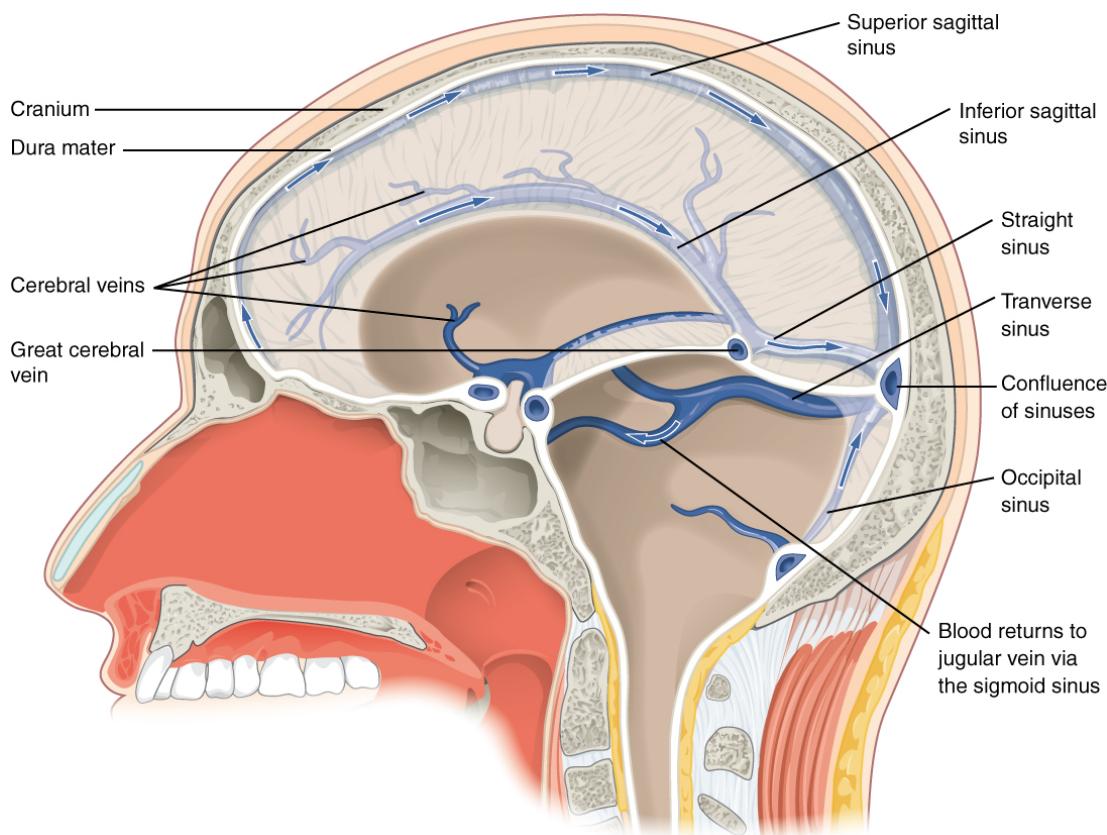


## INTERACTIVE LINK

Watch this [animation](http://openstax.org/l/bloodflow1) (<http://openstax.org/l/bloodflow1>) to see how blood flows to the brain and passes through the circle of Willis before being distributed through the cerebrum. The circle of Willis is a specialized arrangement of arteries that ensure constant perfusion of the cerebrum even in the event of a blockage of one of the arteries in the circle. The animation shows the normal direction of flow through the circle of Willis to the middle cerebral artery. Where would the blood come from if there were a blockage just posterior to the middle cerebral artery on the left?

### Venous Return

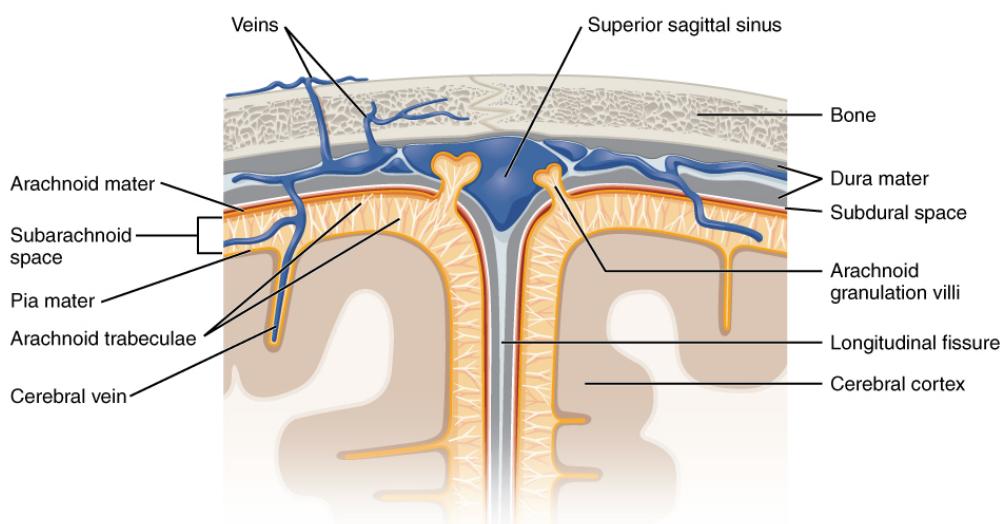
After passing through the CNS, blood returns to the circulation through a series of **dural sinuses** and veins (Figure 13.16). The **superior sagittal sinus** runs in the groove of the longitudinal fissure, where it absorbs CSF from the meninges. The superior sagittal sinus drains to the confluence of sinuses, along with the **occipital sinuses** and **straight sinus**, to then drain into the **transverse sinuses**. The transverse sinuses connect to the **sigmoid sinuses**, which then connect to the **jugular veins**. From there, the blood continues toward the heart to be pumped to the lungs for reoxygenation.



**FIGURE 13.16 Dural Sinuses and Veins** Blood drains from the brain through a series of sinuses that connect to the jugular veins.

### Protective Coverings of the Brain and Spinal Cord

The outer surface of the CNS is covered by a series of membranes composed of connective tissue called the **meninges**, which protect the brain. The **dura mater** is a thick fibrous layer and a strong protective sheath over the entire brain and spinal cord. It is anchored to the inner surface of the cranium and vertebral cavity. The **arachnoid mater** is a membrane of thin fibrous tissue that forms a loose sac around the CNS. Beneath the arachnoid is a thin, filamentous mesh called the **arachnoid trabeculae**, which looks like a spider web, giving this layer its name. Directly adjacent to the surface of the CNS is the **pia mater**, a thin fibrous membrane that follows the convolutions of gyri and sulci in the cerebral cortex and fits into other grooves and indentations (Figure 13.17).



**FIGURE 13.17 Meningeal Layers of Superior Sagittal Sinus** The layers of the meninges in the longitudinal fissure of the superior sagittal sinus are shown, with the dura mater adjacent to the inner surface of the cranium, the pia mater adjacent to the surface of the brain, and the arachnoid and subarachnoid space between them. An arachnoid villus is shown emerging into the dural sinus to allow CSF to filter back into the blood for drainage.

### Dura Mater

Like a thick cap covering the brain, the dura mater is a tough outer covering. The name comes from the Latin for “tough mother” to represent its physically protective role. It encloses the entire CNS and the major blood vessels that enter the cranium and vertebral cavity. It is directly attached to the inner surface of the bones of the cranium and to the very end of the vertebral cavity.

There are infoldings of the dura that fit into large crevasses of the brain. Two infoldings go through the midline separations of the cerebrum and cerebellum; one forms a shelf-like tent between the occipital lobes of the cerebrum and the cerebellum, and the other surrounds the pituitary gland. The dura also surrounds and supports the venous sinuses.

### Arachnoid Mater

The middle layer of the meninges is the arachnoid, named for the spider-web–like trabeculae between it and the pia mater. The arachnoid defines a sac-like enclosure around the CNS. The trabeculae are found in the **subarachnoid space**, which is filled with circulating CSF. The arachnoid emerges into the dural sinuses as the **arachnoid granulations**, where the CSF is filtered back into the blood for drainage from the nervous system.

The subarachnoid space is filled with circulating CSF, which also provides a liquid cushion to the brain and spinal cord. Similar to clinical blood work, a sample of CSF can be withdrawn to find chemical evidence of neuropathology or metabolic traces of the biochemical functions of nervous tissue.

### Pia Mater

The outer surface of the CNS is covered in the thin fibrous membrane of the pia mater. It is thought to have a continuous layer of cells providing a fluid-impermeable membrane. The name pia mater comes from the Latin for “tender mother,” suggesting the thin membrane is a gentle covering for the brain. The pia extends into every convolution of the CNS, lining the inside of the sulci in the cerebral and cerebellar cortices. At the end of the spinal cord, a thin filament extends from the inferior end of CNS at the upper lumbar region of the vertebral column to the sacral end of the vertebral column. Because the spinal cord does not extend through the lower lumbar region of the vertebral column, a needle can be inserted through the dura and arachnoid layers to withdraw CSF. This procedure is called a **lumbar puncture** and avoids the risk of damaging the central tissue of the spinal cord. Blood vessels that are nourishing the central nervous tissue are between the pia mater and the nervous tissue.

## Disorders of the...

### Meninges

Meningitis is an inflammation of the meninges, the three layers of fibrous membrane that surround the CNS. Meningitis can be caused by infection by bacteria or viruses. The particular pathogens are not special to meningitis; it is just an inflammation of that specific set of tissues from what might be a broader infection. Bacterial meningitis can be caused by *Streptococcus*, *Staphylococcus*, or the tuberculosis pathogen, among many others. Viral meningitis is usually the result of common enteroviruses (such as those that cause intestinal disorders), but may be the result of the herpes virus or West Nile virus. Bacterial meningitis tends to be more severe.

The symptoms associated with meningitis can be fever, chills, nausea, vomiting, light sensitivity, soreness of the neck, or severe headache. More important are the neurological symptoms, such as changes in mental state (confusion, memory deficits, and other dementia-type symptoms). A serious risk of meningitis can be damage to peripheral structures because of the nerves that pass through the meninges. Hearing loss is a common result of meningitis.

The primary test for meningitis is a lumbar puncture. A needle inserted into the lumbar region of the spinal column through the dura mater and arachnoid membrane into the subarachnoid space can be used to withdraw the fluid for chemical testing. Fatality occurs in 5 to 40 percent of children and 20 to 50 percent of adults with bacterial meningitis. Treatment of bacterial meningitis is through antibiotics, but viral meningitis cannot be treated with antibiotics because viruses do not respond to that type of drug. Fortunately, the viral forms are milder.

### INTERACTIVE LINK

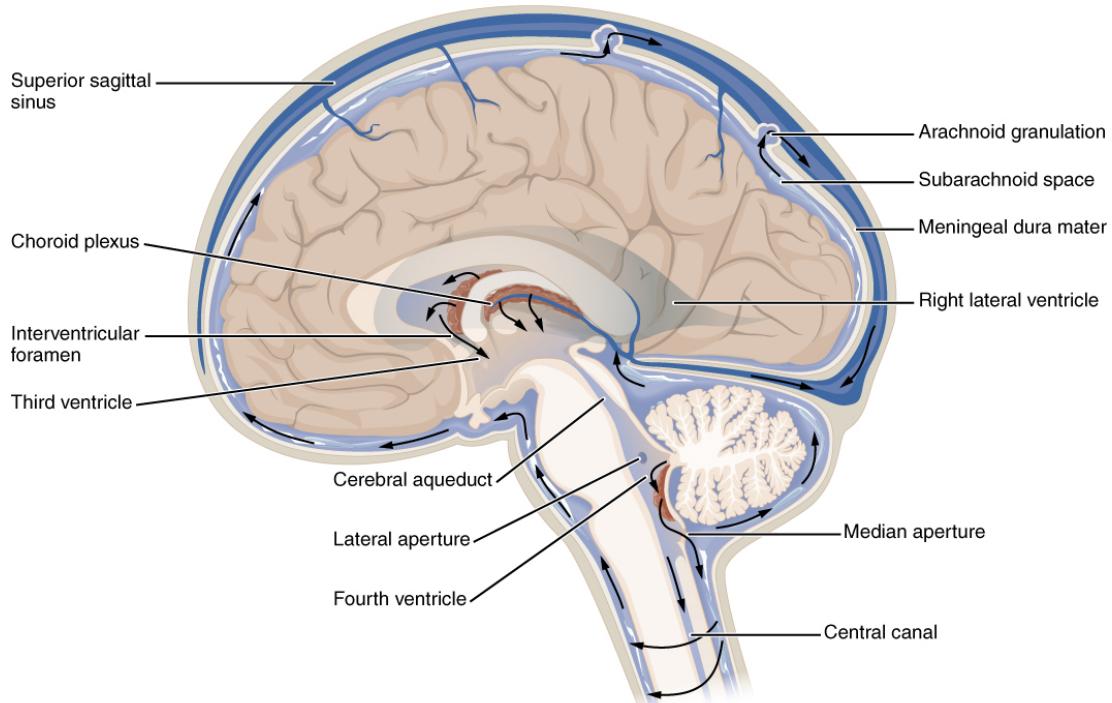
Watch this [video \(<http://openstax.org/l/lumbarpuncture>\)](http://openstax.org/l/lumbarpuncture) that describes the procedure known as the lumbar puncture, a medical procedure used to sample the CSF. Because of the anatomy of the CNS, it is a relative safe location to insert a needle. Why is the lumbar puncture performed in the lower lumbar area of the vertebral column?

## The Ventricular System

Cerebrospinal fluid (CSF) circulates throughout and around the CNS. In other tissues, water and small molecules are filtered through capillaries as the major contributor to the interstitial fluid. In the brain, CSF is produced in special structures to perfuse through the nervous tissue of the CNS and is continuous with the interstitial fluid. Specifically, CSF circulates to remove metabolic wastes from the interstitial fluids of nervous tissues and return them to the blood stream. The **ventricles** are the open spaces within the brain where CSF circulates. In some of these spaces, CSF is produced by filtering of the blood that is performed by a specialized membrane known as a choroid plexus. The CSF circulates through all of the ventricles to eventually emerge into the subarachnoid space where it will be reabsorbed into the blood.

### The Ventricle

There are four ventricles within the brain, all of which developed from the original hollow space within the neural tube, the **central canal**. The first two are named the **lateral ventricles** and are deep within the cerebrum. These ventricles are connected to the **third ventricle** by two openings called the **interventricular foramina**. The third ventricle is the space between the left and right sides of the diencephalon, which opens into the **cerebral aqueduct** that passes through the midbrain. The aqueduct opens into the **fourth ventricle**, which is the space between the cerebellum and the pons and upper medulla ([Figure 13.18](#)).



**FIGURE 13.18 Cerebrospinal Fluid Circulation** The choroid plexus in the four ventricles produce CSF, which is circulated through the ventricular system and then enters the subarachnoid space through the median and lateral apertures. The CSF is then reabsorbed into the blood at the arachnoid granulations, where the arachnoid membrane emerges into the dural sinuses.

As the telencephalon enlarges and grows into the cranial cavity, it is limited by the space within the skull. The telencephalon is the most anterior region of what was the neural tube, but cannot grow past the limit of the frontal bone of the skull. Because the cerebrum fits into this space, it takes on a C-shaped formation, through the frontal, parietal, occipital, and finally temporal regions. The space within the telencephalon is stretched into this same C-shape. The two ventricles are in the left and right sides, and were at one time referred to as the first and second ventricles. The interventricular foramina connect the frontal region of the lateral ventricles with the third ventricle.

The third ventricle is the space bounded by the medial walls of the hypothalamus and thalamus. The two thalamus touch in the center in most brains as the massa intermedia, which is surrounded by the third ventricle. The cerebral aqueduct opens just inferior to the epithalamus and passes through the midbrain. The tectum and tegmentum of the midbrain are the roof and floor of the cerebral aqueduct, respectively. The aqueduct opens up into the fourth ventricle. The floor of the fourth ventricle is the dorsal surface of the pons and upper medulla (that gray matter making a continuation of the tegmentum of the midbrain). The fourth ventricle then narrows into the central canal of the spinal cord.

The ventricular system opens up to the subarachnoid space from the fourth ventricle. The single **median aperture** and the pair of **lateral apertures** connect to the subarachnoid space so that CSF can flow through the ventricles and around the outside of the CNS. Cerebrospinal fluid is produced within the ventricles by a type of specialized membrane called a **choroid plexus**. Ependymal cells (one of the types of glial cells described in the introduction to the nervous system) surround blood capillaries and filter the blood to make CSF. The fluid is a clear solution with a limited amount of the constituents of blood. It is essentially water, small molecules, and electrolytes. Oxygen and carbon dioxide are dissolved into the CSF, as they are in blood, and can diffuse between the fluid and the nervous tissue.

### Cerebrospinal Fluid Circulation

The choroid plexuses are found in all four ventricles. Observed in dissection, they appear as soft, fuzzy structures that may still be pink, depending on how well the circulatory system is cleared in preparation of the tissue. The CSF is produced from components extracted from the blood, so its flow out of the ventricles is tied to the pulse of cardiovascular circulation.

From the lateral ventricles, the CSF flows into the third ventricle, where more CSF is produced, and then through the

cerebral aqueduct into the fourth ventricle where even more CSF is produced. A very small amount of CSF is filtered at any one of the plexuses, for a total of about 500 milliliters daily, but it is continuously made and pulses through the ventricular system, keeping the fluid moving. From the fourth ventricle, CSF can continue down the central canal of the spinal cord, but this is essentially a cul-de-sac, so more of the fluid leaves the ventricular system and moves into the subarachnoid space through the median and lateral apertures.

Within the subarachnoid space, the CSF flows around all of the CNS, providing two important functions. As with elsewhere in its circulation, the CSF picks up metabolic wastes from the nervous tissue and moves it out of the CNS. It also acts as a liquid cushion for the brain and spinal cord. By surrounding the entire system in the subarachnoid space, it provides a thin buffer around the organs within the strong, protective dura mater. The arachnoid granulations are outpocketings of the arachnoid membrane into the dural sinuses so that CSF can be reabsorbed into the blood, along with the metabolic wastes. From the dural sinuses, blood drains out of the head and neck through the jugular veins, along with the rest of the circulation for blood, to be reoxygenated by the lungs and wastes to be filtered out by the kidneys ([Table 13.2](#)).

### **INTERACTIVE LINK**

Watch this [animation](http://openstax.org/l/CSFflow) (<http://openstax.org/l/CSFflow>) that shows the flow of CSF through the brain and spinal cord, and how it originates from the ventricles and then spreads into the space within the meninges, where the fluids then move into the venous sinuses to return to the cardiovascular circulation. What are the structures that produce CSF and where are they found? How are the structures indicated in this animation?

#### Components of CSF Circulation

	Lateral ventricles	Third ventricle	Cerebral aqueduct	Fourth ventricle	Central canal	Subarachnoid space
Location in CNS	Cerebrum	Diencephalon	Midbrain	Between pons/upper medulla and cerebellum	Spinal cord	External to entire CNS
Blood vessel structure	Choroid plexus	Choroid plexus	None	Choroid plexus	None	Arachnoid granulations

**TABLE 13.2**

### **Disorders of the...**

#### **Central Nervous System**

The supply of blood to the brain is crucial to its ability to perform many functions. Without a steady supply of oxygen, and to a lesser extent glucose, the nervous tissue in the brain cannot keep up its extensive electrical activity. These nutrients get into the brain through the blood, and if blood flow is interrupted, neurological function is compromised.

The common name for a disruption of blood supply to the brain is a stroke. It is caused by a blockage to an artery in the brain. The blockage is from some type of embolus: a blood clot, a fat embolus, or an air bubble. When the blood cannot travel through the artery, the surrounding tissue that is deprived starves and dies. Strokes will often result in the loss of very specific functions. A stroke in the lateral medulla, for example, can cause a loss in the ability to swallow. Sometimes, seemingly unrelated functions will be lost because they are dependent on structures in the same region. Along with the swallowing in the previous example, a stroke in that region could affect sensory functions from the face or extremities because important white matter pathways also pass through the lateral medulla. Loss of blood flow to specific regions of the cortex can lead to the loss of specific higher functions, from the ability to recognize faces to the ability to move a particular region of the body.

Severe or limited memory loss can be the result of a temporal lobe stroke.

Related to strokes are transient ischemic attacks (TIAs), which can also be called “mini-strokes.” These are events in which a physical blockage may be temporary, cutting off the blood supply and oxygen to a region, but not to the extent that it causes cell death in that region. While the neurons in that area are recovering from the event, neurological function may be lost. Function can return if the area is able to recover from the event.

Recovery from a stroke (or TIA) is strongly dependent on the speed of treatment. Often, the person who is present and notices something is wrong must then make a decision. The mnemonic **FAST** helps people remember what to look for when someone is dealing with sudden losses of neurological function. If someone complains of feeling “funny,” check these things quickly: Look at the person’s face. Do they have problems moving **F**ace muscles and making regular facial expressions? Ask the person to raise their **A**rms above the head. Can the person lift one arm but not the other? Has the person’s **S**peech changed? Are they slurring words or having trouble saying things? If any of these things have happened, then it is **T**ime to call for help.

Sometimes, treatment with blood-thinning drugs can alleviate the problem, and recovery is possible. If the tissue is damaged, the amazing thing about the nervous system is that it is adaptable. With physical, occupational, and speech therapy, victims of strokes can recover, or more accurately relearn, functions.

## 13.4 The Peripheral Nervous System

### LEARNING OBJECTIVES

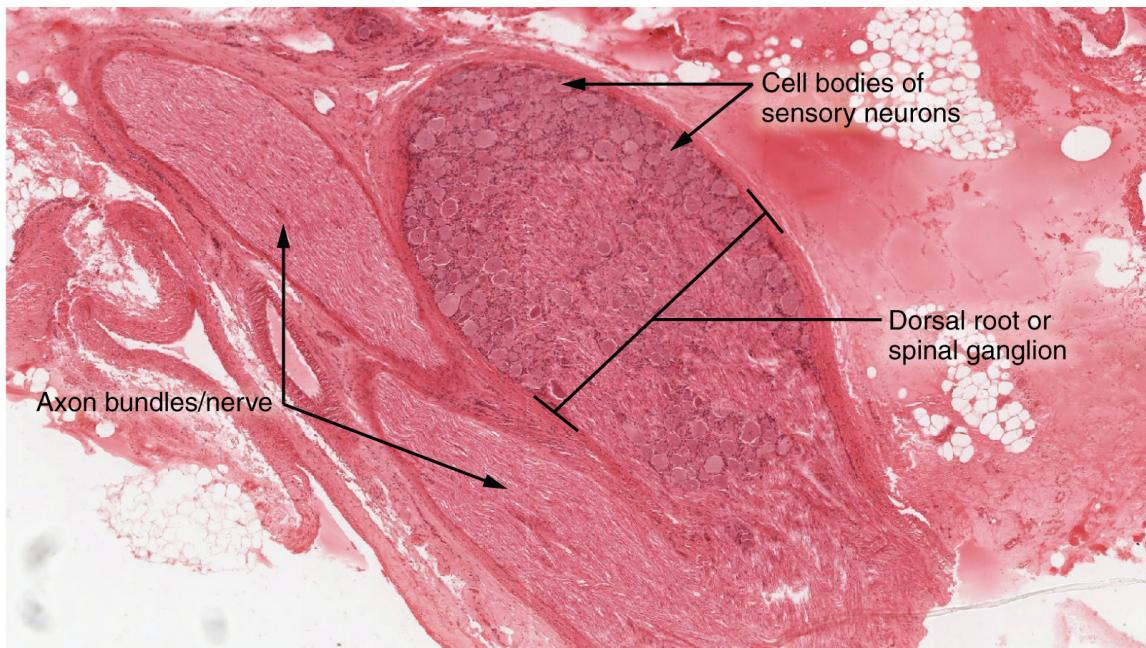
By the end of this section, you will be able to:

- Describe the structures found in the PNS
- Distinguish between somatic and autonomic structures, including the special peripheral structures of the enteric nervous system
- Name the twelve cranial nerves and explain the functions associated with each
- Describe the sensory and motor components of spinal nerves and the plexuses that they pass through

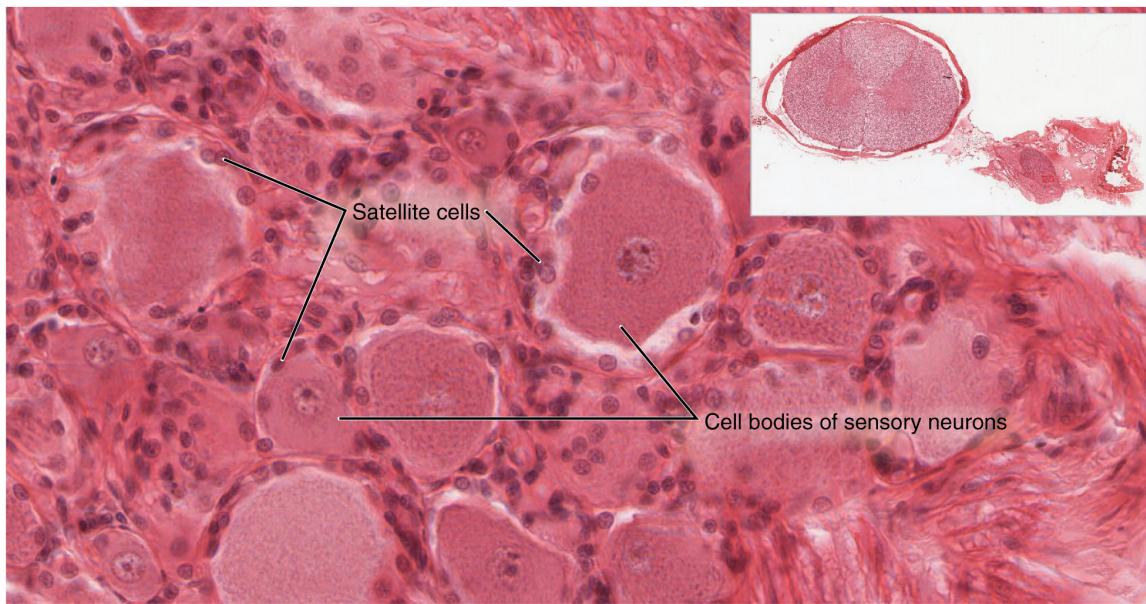
The PNS is not as contained as the CNS because it is defined as everything that is not the CNS. Some peripheral structures are incorporated into the other organs of the body. In describing the anatomy of the PNS, it is necessary to describe the common structures, the nerves and the ganglia, as they are found in various parts of the body. Many of the neural structures that are incorporated into other organs are features of the digestive system; these structures are known as the **enteric nervous system** and are a special subset of the PNS.

### Ganglia

A ganglion is a group of neuron cell bodies in the periphery. Ganglia can be categorized, for the most part, as either sensory ganglia or autonomic ganglia, referring to their primary functions. The most common type of sensory ganglion is a **dorsal (posterior) root ganglion**. These ganglia are the cell bodies of neurons with axons that are sensory endings in the periphery, such as in the skin, and that extend into the CNS through the dorsal nerve root. The ganglion is an enlargement of the nerve root. Under microscopic inspection, it can be seen to include the cell bodies of the neurons, as well as bundles of fibers that are the posterior nerve root ([Figure 13.19](#)). The cells of the dorsal root ganglion are unipolar cells, classifying them by shape. Also, the small round nuclei of satellite cells can be seen surrounding—as if they were orbiting—the neuron cell bodies.



**FIGURE 13.19 Dorsal Root Ganglion** The cell bodies of sensory neurons, which are unipolar neurons by shape, are seen in this photomicrograph. Also, the fibrous region is composed of the axons of these neurons that are passing through the ganglion to be part of the dorsal nerve root (tissue source: canine). LM  $\times 40$ . (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



**FIGURE 13.20 Spinal Cord and Root Ganglion** The slide includes both a cross-section of the lumbar spinal cord and a section of the dorsal root ganglion (see also Figure 13.19) (tissue source: canine). LM  $\times 1600$ . (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

### INTERACTIVE LINK

View the [University of Michigan WebScope](http://openstax.org/l/spinalroot) (<http://openstax.org/l/spinalroot>) to explore the tissue sample in greater detail. If you zoom in on the dorsal root ganglion, you can see smaller satellite glial cells surrounding the large cell bodies of the sensory neurons. From what structure do satellite cells derive during embryologic development?

Another type of sensory ganglion is a **cranial nerve ganglion**. This is analogous to the dorsal root ganglion, except that it is associated with a **cranial nerve** instead of a **spinal nerve**. The roots of cranial nerves are within the cranium, whereas the ganglia are outside the skull. For example, the **trigeminal ganglion** is superficial to the temporal bone whereas its associated nerve is attached to the mid-ppons region of the brain stem. The neurons of

cranial nerve ganglia are also unipolar in shape with associated satellite cells.

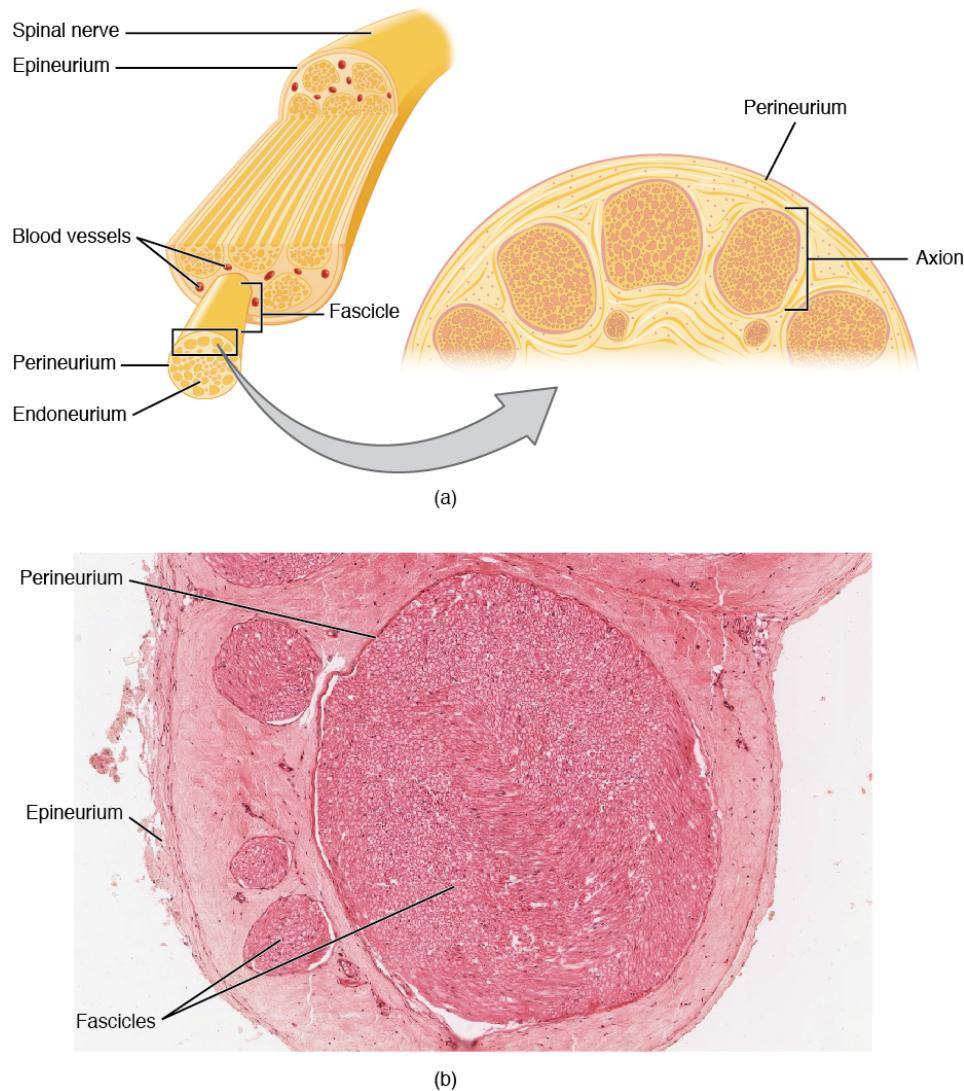
The other major category of ganglia are those of the autonomic nervous system, which is divided into the sympathetic and parasympathetic nervous systems. The **sympathetic chain ganglia** constitute a row of ganglia along the vertebral column that receive central input from the lateral horn of the thoracic and upper lumbar spinal cord. Superior to the chain ganglia are three **paravertebral ganglia** in the cervical region. Three other autonomic ganglia that are related to the sympathetic chain are the **prevertebral ganglia**, which are located outside of the chain but have similar functions. They are referred to as prevertebral because they are anterior to the vertebral column. The neurons of these autonomic ganglia are multipolar in shape, with dendrites radiating out around the cell body where synapses from the spinal cord neurons are made. The neurons of the chain, paravertebral, and prevertebral ganglia then project to organs in the head and neck, thoracic, abdominal, and pelvic cavities to regulate the sympathetic aspect of homeostatic mechanisms.

Another group of autonomic ganglia are the **terminal ganglia** that receive input from cranial nerves or sacral spinal nerves and are responsible for regulating the parasympathetic aspect of homeostatic mechanisms. These two sets of ganglia, sympathetic and parasympathetic, often project to the same organs—one input from the chain ganglia and one input from a terminal ganglion—to regulate the overall function of an organ. For example, the heart receives two inputs such as these; one increases heart rate, and the other decreases it. The terminal ganglia that receive input from cranial nerves are found in the head and neck, as well as the thoracic and upper abdominal cavities, whereas the terminal ganglia that receive sacral input are in the lower abdominal and pelvic cavities.

Terminal ganglia below the head and neck are often incorporated into the wall of the target organ as a **plexus**. A plexus, in a general sense, is a network of fibers or vessels. This can apply to nervous tissue (as in this instance) or structures containing blood vessels (such as a choroid plexus). For example, the **enteric plexus** is the extensive network of axons and neurons in the wall of the small and large intestines. The enteric plexus is actually part of the enteric nervous system, along with the **gastric plexuses** and the **esophageal plexus**. Though the enteric nervous system receives input originating from central neurons of the autonomic nervous system, it does not require CNS input to function. In fact, it operates independently to regulate the digestive system.

## Nerves

Bundles of axons in the PNS are referred to as nerves. These structures in the periphery are different than the central counterpart, called a tract. Nerves are composed of more than just nervous tissue. They have connective tissues invested in their structure, as well as blood vessels supplying the tissues with nourishment. The outer surface of a nerve is a surrounding layer of fibrous connective tissue called the **epineurium**. Within the nerve, axons are further bundled into **fascicles**, which are each surrounded by their own layer of fibrous connective tissue called **perineurium**. Finally, individual axons are surrounded by loose connective tissue called the **endoneurium** ([Figure 13.21](#)). These three layers are similar to the connective tissue sheaths for muscles. Nerves are associated with the region of the CNS to which they are connected, either as cranial nerves connected to the brain or spinal nerves connected to the spinal cord.



**FIGURE 13.21 Nerve Structure** The structure of a nerve is organized by the layers of connective tissue on the outside, around each fascicle, and surrounding the individual nerve fibers (tissue source: simian). LM  $\times 40$ . (Micrograph provided by the Regents of University of Michigan Medical School © 2012)



**FIGURE 13.22 Close-Up of Nerve Trunk** Zoom in on this slide of a nerve trunk to examine the endoneurium, perineurium, and

epineurium in greater detail (tissue source: simian). LM  $\times 1600$ . (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

## INTERACTIVE LINK

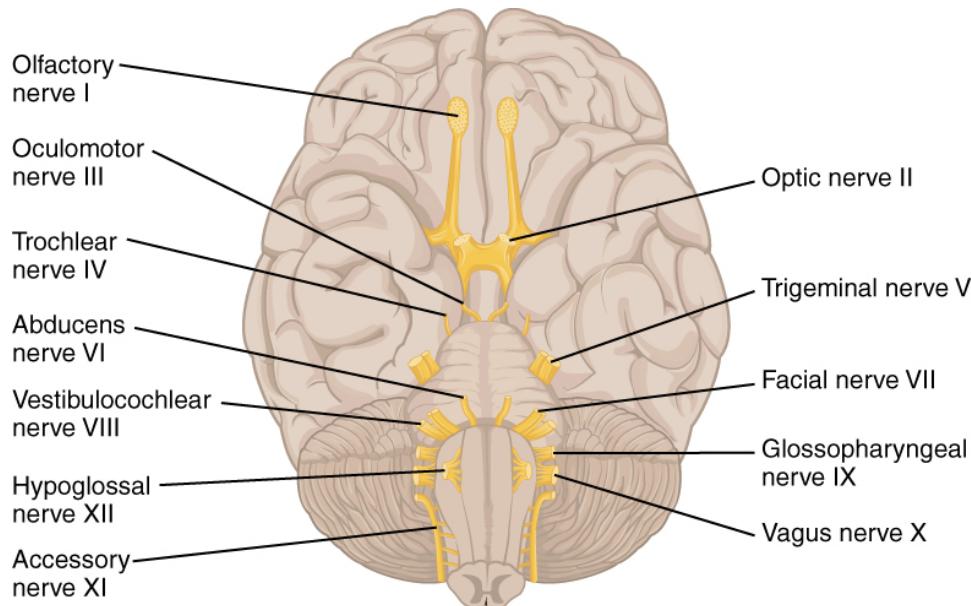
View the [University of Michigan WebScope](http://openstax.org/l/nervetrunk) (<http://openstax.org/l/nervetrunk>) to explore the tissue sample in greater detail. With what structures in a skeletal muscle are the endoneurium, perineurium, and epineurium comparable?

### Cranial Nerves

The nerves attached to the brain are the cranial nerves, which are primarily responsible for the sensory and motor functions of the head and neck (one of these nerves targets organs in the thoracic and abdominal cavities as part of the parasympathetic nervous system). There are twelve cranial nerves, which are designated CN I through CN XII for “Cranial Nerve,” using Roman numerals for 1 through 12. They can be classified as sensory nerves, motor nerves, or a combination of both, meaning that the axons in these nerves originate out of sensory ganglia external to the cranium or motor nuclei within the brain stem. Sensory axons enter the brain to synapse in a nucleus. Motor axons connect to skeletal muscles of the head or neck. Three of the nerves are solely composed of sensory fibers; five are strictly motor; and the remaining four are mixed nerves.

Learning the cranial nerves is a tradition in anatomy courses, and students have always used mnemonic devices to remember the nerve names. A traditional mnemonic is the rhyming couplet, “On Old Olympus’ Towering Tops/A Finn And German Viewed Some Hops,” in which the initial letter of each word corresponds to the initial letter in the name of each nerve. The names of the nerves have changed over the years to reflect current usage and more accurate naming. An exercise to help learn this sort of information is to generate a mnemonic using words that have personal significance. The names of the cranial nerves are listed in [Table 13.3](#) along with a brief description of their function, their source (sensory ganglion or motor nucleus), and their target (sensory nucleus or skeletal muscle). They are listed here with a brief explanation of each nerve ([Figure 13.23](#)).

The **olfactory nerve** and **optic nerve** are responsible for the sense of smell and vision, respectively. The **oculomotor nerve** is responsible for eye movements by controlling four of the **extraocular muscles**. It is also responsible for lifting the upper eyelid when the eyes point up, and for pupillary constriction. The **trochlear nerve** and the **abducens nerve** are both responsible for eye movement, but do so by controlling different extraocular muscles. The **trigeminal nerve** is responsible for cutaneous sensations of the face and controlling the muscles of mastication. The **facial nerve** is responsible for the muscles involved in facial expressions, as well as part of the sense of taste and the production of saliva. The **vestibulocochlear nerve** is responsible for the senses of hearing and balance. The **glossopharyngeal nerve** is responsible for controlling muscles in the oral cavity and upper throat, as well as part of the sense of taste and the production of saliva. The **vagus nerve** is responsible for contributing to homeostatic control of the organs of the thoracic and upper abdominal cavities. The **spinal accessory nerve** is responsible for controlling the muscles of the neck, along with cervical spinal nerves. The **hypoglossal nerve** is responsible for controlling the muscles of the lower throat and tongue.



**FIGURE 13.23 The Cranial Nerves** The anatomical arrangement of the roots of the cranial nerves observed from an inferior view of the brain.

Three of the cranial nerves also contain autonomic fibers, and a fourth is almost purely a component of the autonomic system. The oculomotor, facial, and glossopharyngeal nerves contain fibers that contact autonomic ganglia. The oculomotor fibers initiate pupillary constriction, whereas the facial and glossopharyngeal fibers both initiate salivation. The vagus nerve primarily targets autonomic ganglia in the thoracic and upper abdominal cavities.

### INTERACTIVE LINK

Visit this [site](http://openstax.org/l/NYTmeningitis) (<http://openstax.org/l/NYTmeningitis>) to read about a man who wakes with a headache and a loss of vision. His regular doctor sent him to an ophthalmologist to address the vision loss. The ophthalmologist recognizes a greater problem and immediately sends him to the emergency room. Once there, the patient undergoes a large battery of tests, but a definite cause cannot be found. A specialist recognizes the problem as meningitis, but the question is what caused it originally. How can that be cured? The loss of vision comes from swelling around the optic nerve, which probably presented as a bulge on the inside of the eye. Why is swelling related to meningitis going to push on the optic nerve?

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Another important aspect of the cranial nerves that lends itself to a mnemonic is the functional role each nerve plays. The nerves fall into one of three basic groups. They are sensory, motor, or both (see [Table 13.3](#)). The sentence, “Some Say Marry Money But My Brother Says Brains Beauty Matter More,” corresponds to the basic function of each nerve. The first, second, and eighth nerves are purely sensory: the olfactory (CNI), optic (CNII), and vestibulocochlear (CNVIII) nerves. The three eye-movement nerves are all motor: the oculomotor (CNIII), trochlear (CNIV), and abducens (CNVI). The spinal accessory (CNXI) and hypoglossal (CNXII) nerves are also strictly motor. The remainder of the nerves contain both sensory and motor fibers. They are the trigeminal (CNV), facial (CNVII), glossopharyngeal (CNIX), and vagus (CNX) nerves. The nerves that convey both are often related to each other. The trigeminal and facial nerves both concern the face; one concerns the sensations and the other concerns the muscle movements. The facial and glossopharyngeal nerves are both responsible for conveying gustatory, or taste, sensations as well as controlling salivary glands. The vagus nerve is involved in visceral responses to taste, namely the gag reflex. This is not an exhaustive list of what these combination nerves do, but there is a thread of relation between them.

## Cranial Nerves

Mnemonic	#	Name	Function (S/M/B)	Central connection (nuclei)	Peripheral connection (ganglion or muscle)
On	I	Olfactory	Smell (S)	Olfactory bulb	Olfactory epithelium
Old	II	Optic	Vision (S)	Hypothalamus/ thalamus/midbrain	Retina (retinal ganglion cells)
Olympus'	III	Oculomotor	Eye movements (M)	Oculomotor nucleus	Extraocular muscles (other 4), levator palpebrae superioris, ciliary ganglion (autonomic)
Towering	IV	Trochlear	Eye movements (M)	Trochlear nucleus	Superior oblique muscle
Tops	V	Trigeminal	Sensory/ motor – face (B)	Trigeminal nuclei in the midbrain, pons, and medulla	Trigeminal
A	VI	Abducens	Eye movements (M)	Abducens nucleus	Lateral rectus muscle
Finn	VII	Facial	Motor – face, Taste (B)	Facial nucleus, solitary nucleus, superior salivatory nucleus	Facial muscles, Geniculate ganglion, Pterygopalatine ganglion (autonomic)
And	VIII	Auditory (Vestibulocochlear)	Hearing/ balance (S)	Cochlear nucleus, Vestibular nucleus/ cerebellum	Spiral ganglion (hearing), Vestibular ganglion (balance)
German	IX	Glossopharyngeal	Motor – throat Taste (B)	Solitary nucleus, inferior salivatory nucleus, nucleus ambiguus	Pharyngeal muscles, Geniculate ganglion, Otic ganglion (autonomic)
Viewed	X	Vagus	Motor/ sensory – viscera (autonomic) (B)	Medulla	Terminal ganglia serving thoracic and upper abdominal organs (heart and small intestines)

**TABLE 13.3**

Mnemonic	#	Name	Function (S/M/B)	Central connection (nuclei)	Peripheral connection (ganglion or muscle)
Some	XI	Spinal Accessory	Motor – head and neck (M)	Spinal accessory nucleus	Neck muscles
Hops	XII	Hypoglossal	Motor – lower throat (M)	Hypoglossal nucleus	Muscles of the larynx and lower pharynx

**TABLE 13.3****Spinal Nerves**

The nerves connected to the spinal cord are the spinal nerves. The arrangement of these nerves is much more regular than that of the cranial nerves. All of the spinal nerves are combined sensory and motor axons that separate into two nerve roots. The sensory axons enter the spinal cord as the dorsal nerve root. The motor fibers, both somatic and autonomic, emerge as the ventral nerve root. The dorsal root ganglion for each nerve is an enlargement of the spinal nerve.

There are 31 spinal nerves, named for the level of the spinal cord at which each one emerges. There are eight pairs of cervical nerves designated C1 to C8, twelve thoracic nerves designated T1 to T12, five pairs of lumbar nerves designated L1 to L5, five pairs of sacral nerves designated S1 to S5, and one pair of coccygeal nerves. The nerves are numbered from the superior to inferior positions, and each emerges from the vertebral column through the intervertebral foramen at its level. The first nerve, C1, emerges between the first cervical vertebra and the occipital bone. The second nerve, C2, emerges between the first and second cervical vertebrae. The same occurs for C3 to C7, but C8 emerges between the seventh cervical vertebra and the first thoracic vertebra. For the thoracic and lumbar nerves, each one emerges between the vertebra that has the same designation and the next vertebra in the column. The sacral nerves emerge from the sacral foramina along the length of that unique vertebra.

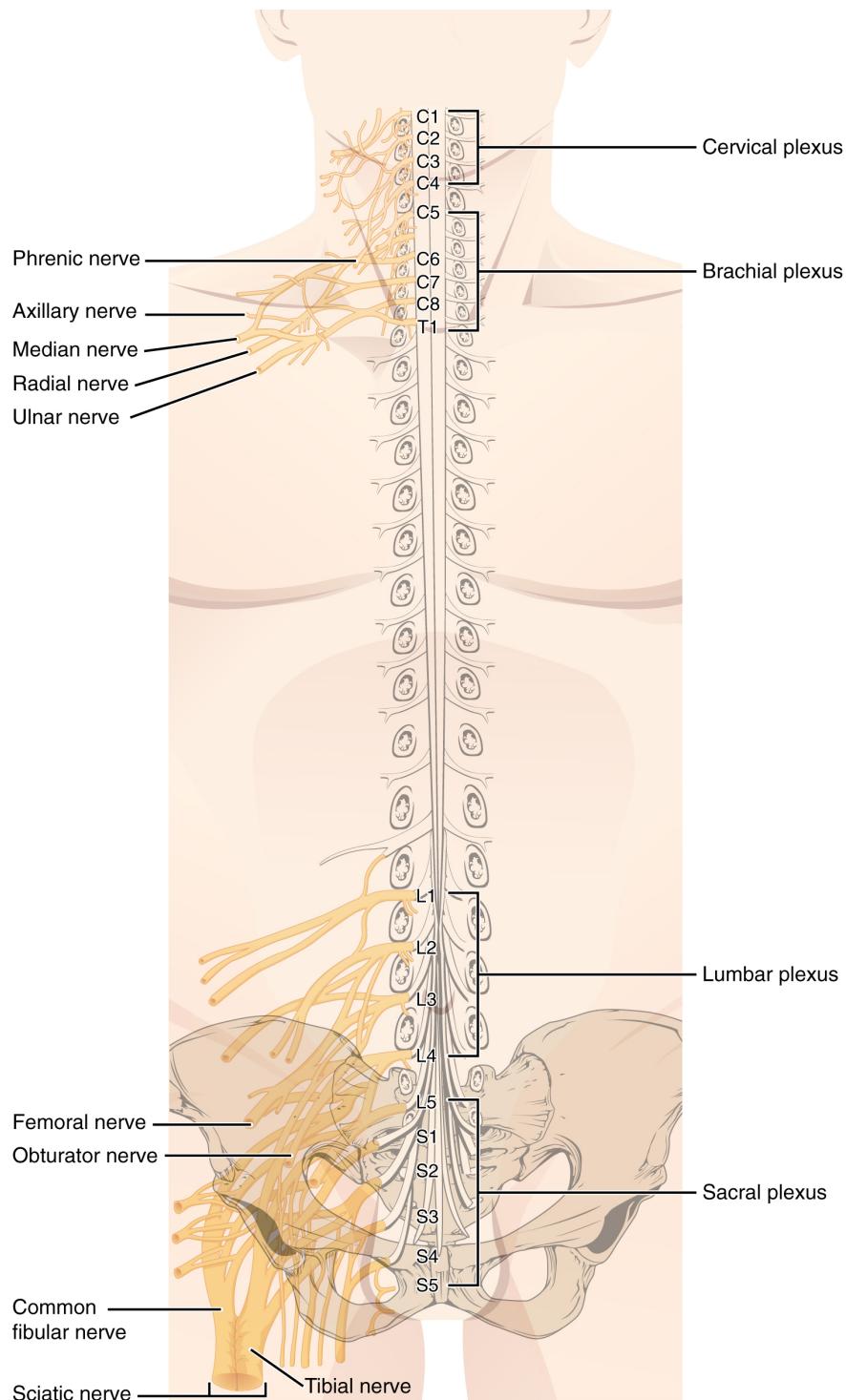
Spinal nerves extend outward from the vertebral column to innervate the periphery. The nerves in the periphery are not straight continuations of the spinal nerves, but rather the reorganization of the axons in those nerves to follow different courses. Axons from different spinal nerves will come together into a **systemic nerve**. This occurs at four places along the length of the vertebral column, each identified as a **nerve plexus**, whereas the other spinal nerves directly correspond to nerves at their respective levels. In this instance, the word plexus is used to describe networks of nerve fibers with no associated cell bodies.

Of the four nerve plexuses, two are found at the cervical level, one at the lumbar level, and one at the sacral level ([Figure 13.24](#)). The **cervical plexus** is composed of axons from spinal nerves C1 through C5 and branches into nerves in the posterior neck and head, as well as the **phrenic nerve**, which connects to the diaphragm at the base of the thoracic cavity. The other plexus from the cervical level is the **brachial plexus**. Spinal nerves C4 through T1 reorganize through this plexus to give rise to the nerves of the arms, as the name brachial suggests. A large nerve from this plexus is the **radial nerve** from which the **axillary nerve** branches to go to the armpit region. The radial nerve continues through the arm and is paralleled by the **ulnar nerve** and the **median nerve**. The **lumbar plexus** arises from all the lumbar spinal nerves and gives rise to nerves innervating the pelvic region and the anterior leg. The **femoral nerve** is one of the major nerves from this plexus, which gives rise to the **saphenous nerve** as a branch that extends through the anterior lower leg. The **sacral plexus** comes from the lower lumbar nerves L4 and L5 and the sacral nerves S1 to S4. The most significant systemic nerve to come from this plexus is the **sciatic nerve**, which is a combination of the **tibial nerve** and the **fibular nerve**. The sciatic nerve extends across the hip joint and is most commonly associated with the condition **sciatica**, which is the result of compression or irritation of the nerve or any of the spinal nerves giving rise to it.

These plexuses are described as arising from spinal nerves and giving rise to certain systemic nerves, but they contain fibers that serve sensory functions or fibers that serve motor functions. This means that some fibers extend from cutaneous or other peripheral sensory surfaces and send action potentials into the CNS. Those are axons of

sensory neurons in the dorsal root ganglia that enter the spinal cord through the dorsal nerve root. Other fibers are the axons of motor neurons of the anterior horn of the spinal cord, which emerge in the ventral nerve root and send action potentials to cause skeletal muscles to contract in their target regions. For example, the radial nerve contains fibers of cutaneous sensation in the arm, as well as motor fibers that move muscles in the arm.

Spinal nerves of the thoracic region, T2 through T11, are not part of the plexuses but rather emerge and give rise to the **intercostal nerves** found between the ribs, which articulate with the vertebrae surrounding the spinal nerve.



**FIGURE 13.24 Nerve Plexuses of the Body** There are four main nerve plexuses in the human body. The cervical plexus supplies nerves to the posterior head and neck, as well as to the diaphragm. The brachial plexus supplies nerves to the arm. The lumbar plexus supplies nerves to the anterior leg. The sacral plexus supplies nerves to the posterior leg.

## Aging and the...

### Nervous System

Anosmia is the loss of the sense of smell. It is often the result of the olfactory nerve being severed, usually because of blunt force trauma to the head. The sensory neurons of the olfactory epithelium have a limited lifespan of approximately one to four months, and new ones are made on a regular basis. The new neurons extend their axons into the CNS by growing along the existing fibers of the olfactory nerve. The ability of these neurons to be replaced is lost with age. Age-related anosmia is not the result of impact trauma to the head, but rather a slow loss of the sensory neurons with no new neurons born to replace them.

Smell is an important sense, especially for the enjoyment of food. There are only five tastes sensed by the tongue, and two of them are generally thought of as unpleasant tastes (sour and bitter). The rich sensory experience of food is the result of odor molecules associated with the food, both as food is moved into the mouth, and therefore passes under the nose, and when it is chewed and molecules are released to move up the pharynx into the posterior nasal cavity. Anosmia results in a loss of the enjoyment of food.

As the replacement of olfactory neurons declines with age, anosmia can set in. Without the sense of smell, many sufferers complain of food tasting bland. Often, the only way to enjoy food is to add seasoning that can be sensed on the tongue, which usually means adding table salt. The problem with this solution, however, is that this increases sodium intake, which can lead to cardiovascular problems through water retention and the associated increase in blood pressure.

## Key Terms

- abducens nerve** sixth cranial nerve; responsible for contraction of one of the extraocular muscles
- alar plate** developmental region of the spinal cord that gives rise to the posterior horn of the gray matter
- amygdala** nucleus deep in the temporal lobe of the cerebrum that is related to memory and emotional behavior
- anterior column** white matter between the anterior horns of the spinal cord composed of many different groups of axons of both ascending and descending tracts
- anterior horn** gray matter of the spinal cord containing multipolar motor neurons, sometimes referred to as the ventral horn
- anterior median fissure** deep midline feature of the anterior spinal cord, marking the separation between the right and left sides of the cord
- anterior spinal artery** blood vessel from the merged branches of the vertebral arteries that runs along the anterior surface of the spinal cord
- arachnoid granulation** outpocket of the arachnoid membrane into the dural sinuses that allows for reabsorption of CSF into the blood
- arachnoid mater** middle layer of the meninges named for the spider-web-like trabeculae that extend between it and the pia mater
- arachnoid trabeculae** filaments between the arachnoid and pia mater within the subarachnoid space
- ascending tract** central nervous system fibers carrying sensory information from the spinal cord or periphery to the brain
- axillary nerve** systemic nerve of the arm that arises from the brachial plexus
- basal forebrain** nuclei of the cerebrum related to modulation of sensory stimuli and attention through broad projections to the cerebral cortex, loss of which is related to Alzheimer's disease
- basal nuclei** nuclei of the cerebrum (with a few components in the upper brain stem and diencephalon) that are responsible for assessing cortical movement commands and comparing them with the general state of the individual through broad modulatory activity of dopamine neurons; largely related to motor functions, as evidenced through the symptoms of Parkinson's and Huntington's diseases
- basal plate** developmental region of the spinal cord that gives rise to the lateral and anterior horns of gray matter
- basilar artery** blood vessel from the merged vertebral arteries that runs along the dorsal surface of the brain stem
- brachial plexus** nerve plexus associated with the lower cervical spinal nerves and first thoracic spinal nerve
- brain stem** region of the adult brain that includes the midbrain, pons, and medulla oblongata and develops from the mesencephalon, metencephalon, and myelencephalon of the embryonic brain
- Broca's area** region of the frontal lobe associated with the motor commands necessary for speech production and located only in the cerebral hemisphere responsible for language production, which is the left side in approximately 95 percent of the population
- Brodmann's areas** mapping of regions of the cerebral cortex based on microscopic anatomy that relates specific areas to functional differences, as described by Brodmann in the early 1900s
- carotid canal** opening in the temporal bone through which the internal carotid artery enters the cranium
- cauda equina** bundle of spinal nerve roots that descend from the lower spinal cord below the first lumbar vertebra and lie within the vertebral cavity; has the appearance of a horse's tail
- caudate** nucleus deep in the cerebrum that is part of the basal nuclei; along with the putamen, it is part of the striatum
- central canal** hollow space within the spinal cord that is the remnant of the center of the neural tube
- central sulcus** surface landmark of the cerebral cortex that marks the boundary between the frontal and parietal lobes
- cephalic flexure** curve in midbrain of the embryo that positions the forebrain ventrally
- cerebellum** region of the adult brain connected primarily to the pons that developed from the metencephalon (along with the pons) and is largely responsible for comparing information from the cerebrum with sensory feedback from the periphery through the spinal cord
- cerebral aqueduct** connection of the ventricular system between the third and fourth ventricles located in the midbrain
- cerebral cortex** outer gray matter covering the forebrain, marked by wrinkles and folds known as gyri and sulci
- cerebral hemisphere** one half of the bilaterally symmetrical cerebrum
- cerebrum** region of the adult brain that develops from the telencephalon and is responsible for higher neurological functions such as memory, emotion,

- and consciousness
- cervical plexus** nerve plexus associated with the upper cervical spinal nerves
- choroid plexus** specialized structures containing ependymal cells lining blood capillaries that filter blood to produce CSF in the four ventricles of the brain
- circle of Willis** unique anatomical arrangement of blood vessels around the base of the brain that maintains perfusion of blood into the brain even if one component of the structure is blocked or narrowed
- common carotid artery** blood vessel that branches off the aorta (or the brachiocephalic artery on the right) and supplies blood to the head and neck
- corpus callosum** large white matter structure that connects the right and left cerebral hemispheres
- cranial nerve** one of twelve nerves connected to the brain that are responsible for sensory or motor functions of the head and neck
- cranial nerve ganglion** sensory ganglion of cranial nerves
- descending tract** central nervous system fibers carrying motor commands from the brain to the spinal cord or periphery
- diencephalon** region of the adult brain that retains its name from embryonic development and includes the thalamus and hypothalamus
- direct pathway** connections within the basal nuclei from the striatum to the globus pallidus internal segment and substantia nigra pars reticulata that disinhibit the thalamus to increase cortical control of movement
- disinhibition** disynaptic connection in which the first synapse inhibits the second cell, which then stops inhibiting the final target
- dorsal (posterior) nerve root** axons entering the posterior horn of the spinal cord
- dorsal (posterior) root ganglion** sensory ganglion attached to the posterior nerve root of a spinal nerve
- dura mater** tough, fibrous, outer layer of the meninges that is attached to the inner surface of the cranium and vertebral column and surrounds the entire CNS
- dural sinus** any of the venous structures surrounding the brain, enclosed within the dura mater, which drain blood from the CNS to the common venous return of the jugular veins
- endoneurium** innermost layer of connective tissue that surrounds individual axons within a nerve
- enteric nervous system** peripheral structures, namely ganglia and nerves, that are incorporated into the digestive system organs
- enteric plexus** neuronal plexus in the wall of the intestines, which is part of the enteric nervous system
- epineurium** outermost layer of connective tissue that surrounds an entire nerve
- epithalamus** region of the diecephalon containing the pineal gland
- esophageal plexus** neuronal plexus in the wall of the esophagus that is part of the enteric nervous system
- extraocular muscles** six skeletal muscles that control eye movement within the orbit
- facial nerve** seventh cranial nerve; responsible for contraction of the facial muscles and for part of the sense of taste, as well as causing saliva production
- fascicle** small bundles of nerve or muscle fibers enclosed by connective tissue
- femoral nerve** systemic nerve of the anterior leg that arises from the lumbar plexus
- fibular nerve** systemic nerve of the posterior leg that begins as part of the sciatic nerve
- foramen magnum** large opening in the occipital bone of the skull through which the spinal cord emerges and the vertebral arteries enter the cranium
- forebrain** anterior region of the adult brain that develops from the prosencephalon and includes the cerebrum and diencephalon
- fourth ventricle** the portion of the ventricular system that is in the region of the brain stem and opens into the subarachnoid space through the median and lateral apertures
- frontal eye field** region of the frontal lobe associated with motor commands to orient the eyes toward an object of visual attention
- frontal lobe** region of the cerebral cortex directly beneath the frontal bone of the cranium
- gastric plexuses** neuronal networks in the wall of the stomach that are part of the enteric nervous system
- globus pallidus** nuclei deep in the cerebrum that are part of the basal nuclei and can be divided into the internal and external segments
- glossopharyngeal nerve** ninth cranial nerve; responsible for contraction of muscles in the tongue and throat and for part of the sense of taste, as well as causing saliva production
- gyrus** ridge formed by convolutions on the surface of the cerebrum or cerebellum
- hindbrain** posterior region of the adult brain that develops from the rhombencephalon and includes the pons, medulla oblongata, and cerebellum
- hippocampus** gray matter deep in the temporal lobe that is very important for long-term memory formation

- hypoglossal nerve** twelfth cranial nerve; responsible for contraction of muscles of the tongue
- hypothalamus** major region of the diencephalon that is responsible for coordinating autonomic and endocrine control of homeostasis
- indirect pathway** connections within the basal nuclei from the striatum through the globus pallidus external segment and subthalamic nucleus to the globus pallidus internal segment/substantia nigra pars compacta that result in inhibition of the thalamus to decrease cortical control of movement
- inferior colliculus** half of the midbrain tectum that is part of the brain stem auditory pathway
- inferior olive** nucleus in the medulla that is involved in processing information related to motor control
- intercostal nerve** systemic nerve in the thoracic cavity that is found between two ribs
- internal carotid artery** branch from the common carotid artery that enters the cranium and supplies blood to the brain
- interventricular foramina** openings between the lateral ventricles and third ventricle allowing for the passage of CSF
- jugular veins** blood vessels that return “used” blood from the head and neck
- kinesthesia** general sensory perception of movement of the body
- lateral apertures** pair of openings from the fourth ventricle to the subarachnoid space on either side and between the medulla and cerebellum
- lateral column** white matter of the spinal cord between the posterior horn on one side and the axons from the anterior horn on the same side; composed of many different groups of axons, of both ascending and descending tracts, carrying motor commands to and from the brain
- lateral horn** region of the spinal cord gray matter in the thoracic, upper lumbar, and sacral regions that is the central component of the sympathetic division of the autonomic nervous system
- lateral sulcus** surface landmark of the cerebral cortex that marks the boundary between the temporal lobe and the frontal and parietal lobes
- lateral ventricles** portions of the ventricular system that are in the region of the cerebrum
- limbic cortex** collection of structures of the cerebral cortex that are involved in emotion, memory, and behavior and are part of the larger limbic system
- limbic system** structures at the edge (limit) of the boundary between the forebrain and hindbrain that are most associated with emotional behavior and memory formation
- longitudinal fissure** large separation along the midline between the two cerebral hemispheres
- lumbar plexus** nerve plexus associated with the lumbar spinal nerves
- lumbar puncture** procedure used to withdraw CSF from the lower lumbar region of the vertebral column that avoids the risk of damaging CNS tissue because the spinal cord ends at the upper lumbar vertebrae
- median aperture** singular opening from the fourth ventricle into the subarachnoid space at the midline between the medulla and cerebellum
- median nerve** systemic nerve of the arm, located between the ulnar and radial nerves
- meninges** protective outer coverings of the CNS composed of connective tissue
- mesencephalon** primary vesicle of the embryonic brain that does not significantly change through the rest of embryonic development and becomes the midbrain
- metencephalon** secondary vesicle of the embryonic brain that develops into the pons and the cerebellum
- midbrain** middle region of the adult brain that develops from the mesencephalon
- myelencephalon** secondary vesicle of the embryonic brain that develops into the medulla
- nerve plexus** network of nerves without neuronal cell bodies included
- neural crest** tissue that detaches from the edges of the neural groove and migrates through the embryo to develop into peripheral structures of both nervous and non-nervous tissues
- neural fold** elevated edge of the neural groove
- neural groove** region of the neural plate that folds into the dorsal surface of the embryo and closes off to become the neural tube
- neural plate** thickened layer of neuroepithelium that runs longitudinally along the dorsal surface of an embryo and gives rise to nervous system tissue
- neural tube** precursor to structures of the central nervous system, formed by the invagination and separation of neuroepithelium
- neuraxis** central axis to the nervous system, from the posterior to anterior ends of the neural tube; the inferior tip of the spinal cord to the anterior surface of the cerebrum
- occipital lobe** region of the cerebral cortex directly beneath the occipital bone of the cranium
- occipital sinuses** dural sinuses along the edge of the occipital lobes of the cerebrum
- oculomotor nerve** third cranial nerve; responsible for contraction of four of the extraocular muscles, the muscle in the upper eyelid, and pupillary

- constriction
- olfaction** special sense responsible for smell, which has a unique, direct connection to the cerebrum
- olfactory nerve** first cranial nerve; responsible for the sense of smell
- optic nerve** second cranial nerve; responsible for visual sensation
- orthostatic reflex** sympathetic function that maintains blood pressure when standing to offset the increased effect of gravity
- paravertebral ganglia** autonomic ganglia superior to the sympathetic chain ganglia
- parietal lobe** region of the cerebral cortex directly beneath the parietal bone of the cranium
- parieto-occipital sulcus** groove in the cerebral cortex representing the border between the parietal and occipital cortices
- perineurium** layer of connective tissue surrounding fascicles within a nerve
- phrenic nerve** systemic nerve from the cervical plexus that innervates the diaphragm
- pia mater** thin, innermost membrane of the meninges that directly covers the surface of the CNS
- plexus** network of nerves or nervous tissue
- postcentral gyrus** primary motor cortex located in the frontal lobe of the cerebral cortex
- posterior columns** white matter of the spinal cord that lies between the posterior horns of the gray matter, sometimes referred to as the dorsal column; composed of axons of ascending tracts that carry sensory information up to the brain
- posterior horn** gray matter region of the spinal cord in which sensory input arrives, sometimes referred to as the dorsal horn
- posterior median sulcus** midline feature of the posterior spinal cord, marking the separation between right and left sides of the cord
- posterolateral sulcus** feature of the posterior spinal cord marking the entry of posterior nerve roots and the separation between the posterior and lateral columns of the white matter
- precentral gyrus** ridge just posterior to the central sulcus, in the parietal lobe, where somatosensory processing initially takes place in the cerebrum
- prefrontal lobe** specific region of the frontal lobe anterior to the more specific motor function areas, which can be related to the early planning of movements and intentions to the point of being personality-type functions
- premotor area** region of the frontal lobe responsible for planning movements that will be executed through the primary motor cortex
- prevertebral ganglia** autonomic ganglia that are anterior to the vertebral column and functionally related to the sympathetic chain ganglia
- primary vesicle** initial enlargements of the anterior neural tube during embryonic development that develop into the forebrain, midbrain, and hindbrain
- proprioception** general sensory perceptions providing information about location and movement of body parts; the “sense of the self”
- prosencephalon** primary vesicle of the embryonic brain that develops into the forebrain, which includes the cerebrum and diencephalon
- putamen** nucleus deep in the cerebrum that is part of the basal nuclei; along with the caudate, it is part of the striatum
- radial nerve** systemic nerve of the arm, the distal component of which is located near the radial bone
- reticular formation** diffuse region of gray matter throughout the brain stem that regulates sleep, wakefulness, and states of consciousness
- rhombencephalon** primary vesicle of the embryonic brain that develops into the hindbrain, which includes the pons, cerebellum, and medulla
- sacral plexus** nerve plexus associated with the lower lumbar and sacral spinal nerves
- saphenous nerve** systemic nerve of the lower anterior leg that is a branch from the femoral nerve
- sciatic nerve** systemic nerve from the sacral plexus that is a combination of the tibial and fibular nerves and extends across the hip joint and gluteal region into the upper posterior leg
- sciatica** painful condition resulting from inflammation or compression of the sciatic nerve or any of the spinal nerves that contribute to it
- secondary vesicle** five vesicles that develop from primary vesicles, continuing the process of differentiation of the embryonic brain
- sigmoid sinuses** dural sinuses that drain directly into the jugular veins
- somatosensation** general senses related to the body, usually thought of as the senses of touch, which would include pain, temperature, and proprioception
- spinal accessory nerve** eleventh cranial nerve; responsible for contraction of neck muscles
- spinal nerve** one of 31 nerves connected to the spinal cord
- straight sinus** dural sinus that drains blood from the deep center of the brain to collect with the other sinuses
- striatum** the caudate and putamen collectively, as part of the basal nuclei, which receive input from the cerebral cortex
- subarachnoid space** space between the arachnoid

mater and pia mater that contains CSF and the fibrous connections of the arachnoid trabeculae

**subcortical nucleus** all the nuclei beneath the cerebral cortex, including the basal nuclei and the basal forebrain

**substantia nigra pars compacta** nuclei within the basal nuclei that release dopamine to modulate the function of the striatum; part of the motor pathway

**substantia nigra pars reticulata** nuclei within the basal nuclei that serve as an output center of the nuclei; part of the motor pathway

**subthalamus** nucleus within the basal nuclei that is part of the indirect pathway

**sulcus** groove formed by convolutions in the surface of the cerebral cortex

**superior colliculus** half of the midbrain tectum that is responsible for aligning visual, auditory, and somatosensory spatial perceptions

**superior sagittal sinus** dural sinus that runs along the top of the longitudinal fissure and drains blood from the majority of the outer cerebrum

**sympathetic chain ganglia** autonomic ganglia in a chain along the anterolateral aspect of the vertebral column that are responsible for contributing to homeostatic mechanisms of the autonomic nervous system

**systemic nerve** nerve in the periphery distal to a nerve plexus or spinal nerve

**tectum** region of the midbrain, thought of as the roof of the cerebral aqueduct, which is subdivided into the inferior and superior colliculi

**tegmentum** region of the midbrain, thought of as the floor of the cerebral aqueduct, which continues into the pons and medulla as the floor of the fourth ventricle

**telencephalon** secondary vesicle of the embryonic brain that develops into the cerebrum

**temporal lobe** region of the cerebral cortex directly beneath the temporal bone of the cranium

## Chapter Review

### 13.1 The Embryologic Perspective

The development of the nervous system starts early in embryonic development. The outer layer of the embryo, the ectoderm, gives rise to the skin and the nervous system. A specialized region of this layer, the neuroectoderm, becomes a groove that folds in and becomes the neural tube beneath the dorsal surface of the embryo. The anterior end of the neural tube develops into the brain, and the posterior region becomes the spinal cord. Tissues at the edges of the neural groove, when it closes off, are called the neural crest and migrate through the embryo to give rise to

**terminal ganglion** autonomic ganglia that are near or within the walls of organs that are responsible for contributing to homeostatic mechanisms of the autonomic nervous system

**thalamus** major region of the diencephalon that is responsible for relaying information between the cerebrum and the hindbrain, spinal cord, and periphery

**third ventricle** portion of the ventricular system that is in the region of the diencephalon

**tibial nerve** systemic nerve of the posterior leg that begins as part of the sciatic nerve

**transverse sinuses** dural sinuses that drain along either side of the occipital–cerebellar space

**trigeminal ganglion** sensory ganglion that contributes sensory fibers to the trigeminal nerve

**trigeminal nerve** fifth cranial nerve; responsible for cutaneous sensation of the face and contraction of the muscles of mastication

**trochlear nerve** fourth cranial nerve; responsible for contraction of one of the extraocular muscles

**ulnar nerve** systemic nerve of the arm located close to the ulna, a bone of the forearm

**vagus nerve** tenth cranial nerve; responsible for the autonomic control of organs in the thoracic and upper abdominal cavities

**ventral (anterior) nerve root** axons emerging from the anterior or lateral horns of the spinal cord

**ventricles** remnants of the hollow center of the neural tube that are spaces for cerebrospinal fluid to circulate through the brain

**vertebral arteries** arteries that ascend along either side of the vertebral column through the transverse foramina of the cervical vertebrae and enter the cranium through the foramen magnum

**vestibulocochlear nerve** eighth cranial nerve; responsible for the sensations of hearing and balance

PNS structures as well as some non-nervous tissues.

The brain develops from this early tube structure and gives rise to specific regions of the adult brain. As the neural tube grows and differentiates, it enlarges into three vesicles that correspond to the forebrain, midbrain, and hindbrain regions of the adult brain. Later in development, two of these three vesicles differentiate further, resulting in five vesicles. Those five vesicles can be aligned with the four major regions of the adult brain. The cerebrum is formed directly from the telencephalon. The diencephalon is the only region that keeps its embryonic name. The

mesencephalon, metencephalon, and myelencephalon become the brain stem. The cerebellum also develops from the metencephalon and is a separate region of the adult brain.

The spinal cord develops out of the rest of the neural tube and retains the tube structure, with the nervous tissue thickening and the hollow center becoming a very small central canal through the cord. The rest of the hollow center of the neural tube corresponds to open spaces within the brain called the ventricles, where cerebrospinal fluid is found.

### 13.2 The Central Nervous System

The adult brain is separated into four major regions: the cerebrum, the diencephalon, the brain stem, and the cerebellum. The cerebrum is the largest portion and contains the cerebral cortex and subcortical nuclei. It is divided into two halves by the longitudinal fissure.

The cortex is separated into the frontal, parietal, temporal, and occipital lobes. The frontal lobe is responsible for motor functions, from planning movements through executing commands to be sent to the spinal cord and periphery. The most anterior portion of the frontal lobe is the prefrontal cortex, which is associated with aspects of personality through its influence on motor responses in decision-making.

The other lobes are responsible for sensory functions. The parietal lobe is where somatosensation is processed. The occipital lobe is where visual processing begins, although the other parts of the brain can contribute to visual function. The temporal lobe contains the cortical area for auditory processing, but also has regions crucial for memory formation.

Nuclei beneath the cerebral cortex, known as the subcortical nuclei, are responsible for augmenting cortical functions. The basal nuclei receive input from cortical areas and compare it with the general state of the individual through the activity of a dopamine-releasing nucleus. The output influences the activity of part of the thalamus that can then increase or decrease cortical activity that often results in changes to motor commands. The basal forebrain is responsible for modulating cortical activity in attention and memory. The limbic system includes deep cerebral nuclei that are responsible for emotion and memory.

The diencephalon includes the thalamus and the hypothalamus, along with some other structures. The thalamus is a relay between the cerebrum and the rest of the nervous system. The hypothalamus coordinates homeostatic functions through the autonomic and endocrine systems.

The brain stem is composed of the midbrain, pons, and medulla. It controls the head and neck region of the body through the cranial nerves. There are control centers in the brain stem that regulate the cardiovascular and respiratory systems.

The cerebellum is connected to the brain stem, primarily at the pons, where it receives a copy of the descending input from the cerebrum to the spinal cord. It can compare this with sensory feedback input through the medulla and send output through the midbrain that can correct motor commands for coordination.

### 13.3 Circulation and the Central Nervous System

The CNS has a privileged blood supply established by the blood-brain barrier. Establishing this barrier are anatomical structures that help to protect and isolate the CNS. The arterial blood to the brain comes from the internal carotid and vertebral arteries, which both contribute to the unique circle of Willis that provides constant perfusion of the brain even if one of the blood vessels is blocked or narrowed. That blood is eventually filtered to make a separate medium, the CSF, that circulates within the spaces of the brain and then into the surrounding space defined by the meninges, the protective covering of the brain and spinal cord.

The blood that nourishes the brain and spinal cord is behind the glial-cell-enforced blood-brain barrier, which limits the exchange of material from blood vessels with the interstitial fluid of the nervous tissue. Thus, metabolic wastes are collected in cerebrospinal fluid that circulates through the CNS. This fluid is produced by filtering blood at the choroid plexuses in the four ventricles of the brain. It then circulates through the ventricles and into the subarachnoid space, between the pia mater and the arachnoid mater. From the arachnoid granulations, CSF is reabsorbed into the blood, removing the waste from the privileged central nervous tissue.

The blood, now with the reabsorbed CSF, drains out of the cranium through the dural sinuses. The dura mater is the tough outer covering of the CNS, which is anchored to the inner surface of the cranial and vertebral cavities. It surrounds the venous space known as the dural sinuses, which connect to the jugular veins, where blood drains from the head and neck.

### 13.4 The Peripheral Nervous System

The PNS is composed of the groups of neurons

(ganglia) and bundles of axons (nerves) that are outside of the brain and spinal cord. Ganglia are of two types, sensory or autonomic. Sensory ganglia contain unipolar sensory neurons and are found on the dorsal root of all spinal nerves as well as associated with many of the cranial nerves. Autonomic ganglia are in the sympathetic chain, the associated paravertebral or prevertebral ganglia, or in terminal ganglia near or within the organs controlled by the autonomic nervous system.

Nerves are classified as cranial nerves or spinal nerves on the basis of their connection to the brain or spinal cord, respectively. The twelve cranial nerves can be

## Interactive Link Questions

1. Watch this [animation](http://openstax.org/l/braindevel) (<http://openstax.org/l/braindevel>) to examine the development of the brain, starting with the neural tube. As the anterior end of the neural tube develops, it enlarges into the primary vesicles that establish the forebrain, midbrain, and hindbrain. Those structures continue to develop throughout the rest of embryonic development and into adolescence. They are the basis of the structure of the fully developed adult brain. How would you describe the difference in the relative sizes of the three regions of the brain when comparing the early (25th embryonic day) brain and the adult brain?
2. Watch this [video](http://openstax.org/l/whitematter) (<http://openstax.org/l/whitematter>) to learn about the white matter in the cerebrum that develops during childhood and adolescence. This is a composite of MRI images taken of the brains of people from 5 years of age through 20 years of age, demonstrating how the cerebrum changes. As the color changes to blue, the ratio of gray matter to white matter changes. The caption for the video describes it as “less gray matter,” which is another way of saying “more white matter.” If the brain does not finish developing until approximately 20 years of age, can teenagers be held responsible for behaving badly?
3. Watch this [video](http://openstax.org/l/basalnuclei1) (<http://openstax.org/l/basalnuclei1>) to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the direct pathway is the shorter pathway through the system that results in increased activity in the cerebral cortex and increased motor activity. The direct pathway is described as resulting in “disinhibition” of the thalamus. What does disinhibition mean? What are the two neurons doing individually to cause this?
4. Watch this [video](http://openstax.org/l/basalnuclei2) (<http://openstax.org/l/basalnuclei2>) to learn about the basal nuclei (also known as the basal ganglia), which have two pathways that process information within the cerebrum. As shown in this video, the indirect pathway is the longer pathway through the system that results in decreased activity in the cerebral cortex, and therefore less motor activity. The indirect pathway has an extra couple of connections in it, including disinhibition of the subthalamic nucleus. What is the end result on the thalamus, and therefore on movement initiated by the cerebral cortex?
5. Watch this [video](http://openstax.org/l/graymatter) (<http://openstax.org/l/graymatter>) to learn about the gray matter of the spinal cord that receives input from fibers of the dorsal (posterior) root and sends information out through the fibers of the ventral (anterior) root. As discussed in this video, these connections represent the interactions of the CNS with peripheral structures for both sensory and motor functions. The cervical and lumbar spinal cords have enlargements as a result of larger populations of neurons. What are these enlargements responsible for?

strictly sensory in function, strictly motor in function, or a combination of the two functions. Sensory fibers are axons of sensory ganglia that carry sensory information into the brain and target sensory nuclei. Motor fibers are axons of motor neurons in motor nuclei of the brain stem and target skeletal muscles of the head and neck. Spinal nerves are all mixed nerves with both sensory and motor fibers. Spinal nerves emerge from the spinal cord and reorganize through plexuses, which then give rise to systemic nerves. Thoracic spinal nerves are not part of any plexus, but give rise to the intercostal nerves directly.

6. Compared with the nearest evolutionary relative, the chimpanzee, the human has a brain that is huge. At a point in the past, a common ancestor gave rise to the two species of humans and chimpanzees. That evolutionary history is long and is still an area of intense study. But something happened to increase the size of the human brain relative to the chimpanzee. Read this [article](http://openstax.org/l/hugebrain) (<http://openstax.org/l/hugebrain>) in which the author explores the current understanding of why this happened.
- According to one hypothesis about the expansion of brain size, what tissue might have been sacrificed so energy was available to grow our larger brain? Based on what you know about that tissue and nervous tissue, why would there be a trade-off between them in terms of energy use?
7. Watch this [animation](http://openstax.org/l/bloodflow1) (<http://openstax.org/l/bloodflow1>) to see how blood flows to the brain and passes through the circle of Willis before being distributed through the cerebrum. The circle of Willis is a specialized arrangement of arteries that ensure constant perfusion of the cerebrum even in the event of a blockage of one of the arteries in the circle. The animation shows the normal direction of flow through the circle of Willis to the middle cerebral artery. Where would the blood come from if there were a blockage just posterior to the middle cerebral artery on the left?
8. Watch this [video](http://openstax.org/l/lumbarpuncture) (<http://openstax.org/l/lumbarpuncture>) that describes the procedure known as the lumbar puncture, a medical procedure used to sample the CSF. Because of the anatomy of the CNS, it is a relatively safe location to insert a needle. Why is the lumbar puncture performed in the lower lumbar area of the vertebral column?
9. Watch this [animation](http://openstax.org/l/CSFflow) (<http://openstax.org/l/CSFflow>) that shows the flow of CSF through the brain and spinal cord, and how it originates from the ventricles and then spreads into the space within the meninges, where the fluids then move into the venous sinuses to return to the cardiovascular circulation. What are the structures that produce CSF and where are they found? How are the structures indicated in this animation?
10. [Figure 13.20](#) If you zoom in on the DRG, you can see smaller satellite glial cells surrounding the large cell bodies of the sensory neurons. From what structure do satellite cells derive during embryologic development?
11. [Figure 13.22](#) To what structures in a skeletal muscle are the endoneurium, perineurium, and epineurium comparable?
12. Visit this [site](http://openstax.org/l/NYTmeningitis) (<http://openstax.org/l/NYTmeningitis>) to read about a man who wakes with a headache and a loss of vision. His regular doctor sent him to an ophthalmologist to address the vision loss. The ophthalmologist recognizes a greater problem and immediately sends him to the emergency room. Once there, the patient undergoes a large battery of tests, but a definite cause cannot be found. A specialist recognizes the problem as meningitis, but the question is what caused it originally. How can that be cured? The loss of vision comes from swelling around the optic nerve, which probably presented as a bulge on the inside of the eye. Why is swelling related to meningitis going to push on the optic nerve?

## Review Questions

13. Aside from the nervous system, which other organ system develops out of the ectoderm?
- digestive
  - respiratory
  - integumentary
  - urinary
14. Which primary vesicle of the embryonic nervous system does not differentiate into more vesicles at the secondary stage?
- prosencephalon
  - mesencephalon
  - diencephalon
  - rhombencephalon
15. Which adult structure(s) arises from the diencephalon?
- thalamus, hypothalamus, retina
  - midbrain, pons, medulla
  - pons and cerebellum
  - cerebrum
16. Which non-nervous tissue develops from the neuroectoderm?
- respiratory mucosa
  - vertebral bone
  - digestive lining
  - craniofacial bone

- 17.** Which structure is associated with the embryologic development of the peripheral nervous system?
- neural crest
  - neuraxis
  - rhombencephalon
  - neural tube
- 18.** Which lobe of the cerebral cortex is responsible for generating motor commands?
- temporal
  - parietal
  - occipital
  - frontal
- 19.** What region of the diencephalon coordinates homeostasis?
- thalamus
  - epithalamus
  - hypothalamus
  - subthalamus
- 20.** What level of the brain stem is the major input to the cerebellum?
- midbrain
  - pons
  - medulla
  - spinal cord
- 21.** What region of the spinal cord contains motor neurons that direct the movement of skeletal muscles?
- anterior horn
  - posterior horn
  - lateral horn
  - alar plate
- 22.** Brodmann's areas map different regions of the \_\_\_\_\_ to particular functions.
- cerebellum
  - cerebral cortex
  - basal forebrain
  - corpus callosum
- 23.** What blood vessel enters the cranium to supply the brain with fresh, oxygenated blood?
- common carotid artery
  - jugular vein
  - internal carotid artery
  - aorta
- 24.** Which layer of the meninges surrounds and supports the sinuses that form the route through which blood drains from the CNS?
- dura mater
  - arachnoid mater
  - subarachnoid
  - pia mater
- 25.** What type of glial cell is responsible for filtering blood to produce CSF at the choroid plexus?
- ependymal cell
  - astrocyte
  - oligodendrocyte
  - Schwann cell
- 26.** Which portion of the ventricular system is found within the diencephalon?
- lateral ventricles
  - third ventricle
  - cerebral aqueduct
  - fourth ventricle
- 27.** What condition causes a stroke?
- inflammation of meninges
  - lumbar puncture
  - infection of cerebral spinal fluid
  - disruption of blood to the brain
- 28.** What type of ganglion contains neurons that control homeostatic mechanisms of the body?
- sensory ganglion
  - dorsal root ganglion
  - autonomic ganglion
  - cranial nerve ganglion
- 29.** Which ganglion is responsible for cutaneous sensations of the face?
- otic ganglion
  - vestibular ganglion
  - geniculate ganglion
  - trigeminal ganglion
- 30.** What is the name for a bundle of axons within a nerve?
- fascicle
  - tract
  - nerve root
  - epineurium
- 31.** Which cranial nerve does not control functions in the head and neck?
- olfactory
  - trochlear
  - glossopharyngeal
  - vagus

- 32.** Which of these structures is not under direct control of the peripheral nervous system?
- trigeminal ganglion
  - gastric plexus
  - sympathetic chain ganglia
  - cervical plexus

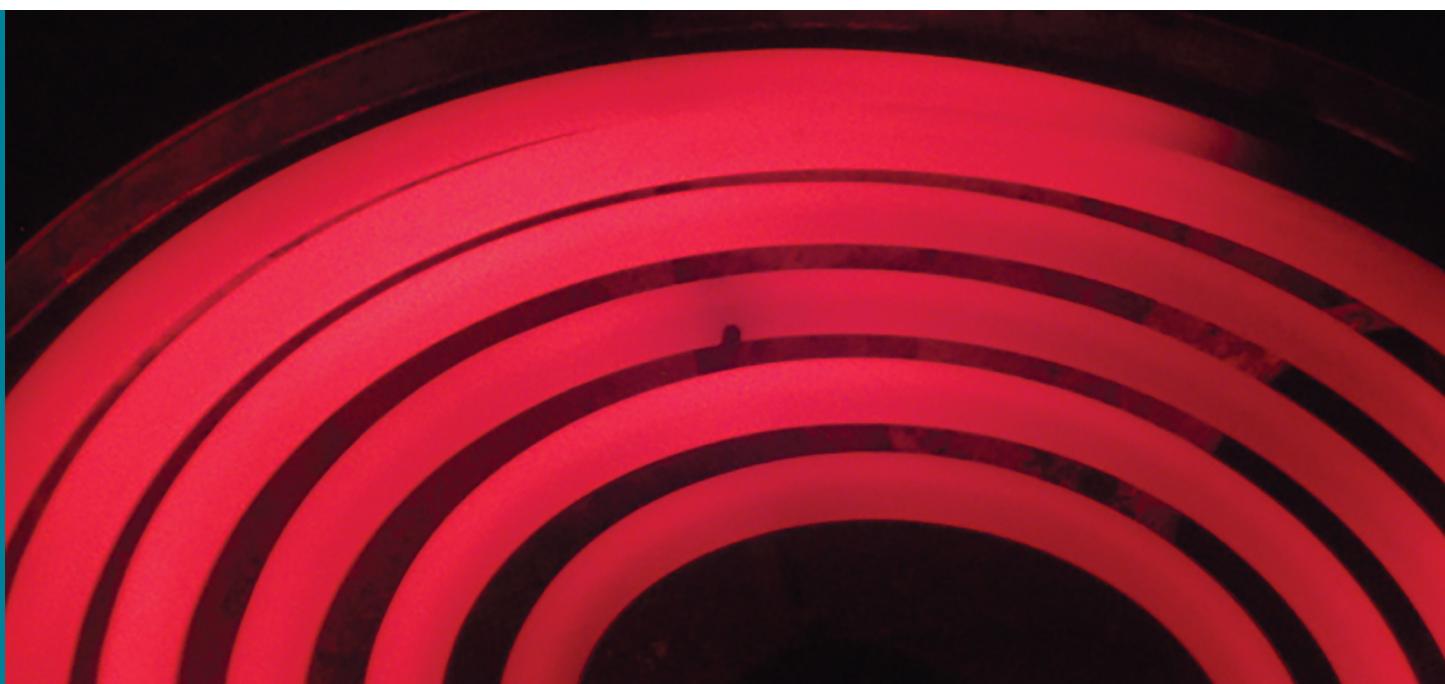
## Critical Thinking Questions

- 33.** Studying the embryonic development of the nervous system makes it easier to understand the complexity of the adult nervous system. Give one example of how development in the embryonic nervous system explains a more complex structure in the adult nervous system.
- 34.** What happens in development that suggests that there is a special relationship between the skeletal structure of the head and the nervous system?
- 35.** Damage to specific regions of the cerebral cortex, such as through a stroke, can result in specific losses of function. What functions would likely be lost by a stroke in the temporal lobe?
- 36.** Why do the anatomical inputs to the cerebellum suggest that it can compare motor commands and sensory feedback?
- 37.** Why can the circle of Willis maintain perfusion of the brain even if there is a blockage in one part of the structure?
- 38.** Meningitis is an inflammation of the meninges that can have severe effects on neurological function. Why is infection of this structure potentially so dangerous?
- 39.** Why are ganglia and nerves not surrounded by protective structures like the meninges of the CNS?
- 40.** Testing for neurological function involves a series of tests of functions associated with the cranial nerves. What functions, and therefore which nerves, are being tested by asking a patient to follow the tip of a pen with their eyes?



# CHAPTER 14

## The Somatic Nervous System



**Figure 14.1 Too Hot to Touch** When high temperature is sensed in the skin, a reflexive withdrawal is initiated by the muscles of the arm. Sensory neurons are activated by a stimulus, which is sent to the central nervous system, and a motor response is sent out to the skeletal muscles that control this movement.

### CHAPTER OBJECTIVES

After studying this chapter, you will be able to:

- Describe the components of the somatic nervous system
- Name the modalities and submodalities of the sensory systems
- Distinguish between general and special senses
- Describe regions of the central nervous system that contribute to somatic functions
- Explain the stimulus-response motor pathway

**INTRODUCTION** The somatic nervous system is traditionally considered a division within the peripheral nervous system. However, this misses an important point: somatic refers to a functional division, whereas peripheral refers to an anatomic division. The somatic nervous system is responsible for our conscious perception of the environment and for our voluntary responses to that perception by means of skeletal muscles. Peripheral sensory neurons receive input from environmental stimuli, but the neurons that produce motor responses originate in the central nervous system. The distinction between the structures (i.e., anatomy) of the peripheral and central nervous systems and functions (i.e., physiology) of the somatic and autonomic systems can most easily be demonstrated through a simple reflex action. When you touch a hot stove, you pull your hand away. Sensory receptors in the skin sense extreme temperature and the early signs of tissue damage. This triggers an action potential, which travels along the sensory fiber from the skin, through the dorsal spinal root to the spinal cord, and directly activates a ventral horn motor neuron. That neuron sends a signal along its axon to excite the biceps brachii, causing contraction of the muscle and flexion of the forearm at the elbow to withdraw the hand from the hot stove. The withdrawal reflex has more components, such as inhibiting the opposing muscle and balancing posture while the arm is forcefully withdrawn, which will be further explored at the end of this chapter.

The basic withdrawal reflex explained above includes sensory input (the painful stimulus), central processing (the synapse in the spinal cord), and motor output (activation of a ventral motor neuron that causes contraction of the biceps brachii). Expanding the explanation of the withdrawal reflex can include inhibition of the opposing muscle, or cross extension, either of which increase the complexity of the example by involving more central neurons. A

collateral branch of the sensory axon would inhibit another ventral horn motor neuron so that the triceps brachii do not contract and slow the withdrawal down. The cross extensor reflex provides a counterbalancing movement on the other side of the body, which requires another collateral of the sensory axon to activate contraction of the extensor muscles in the contralateral limb.

A more complex example of somatic function is conscious muscle movement. For example, reading of this text starts with visual sensory input to the retina, which then projects to the thalamus, and on to the cerebral cortex. A sequence of regions of the cerebral cortex process the visual information, starting in the primary visual cortex of the occipital lobe, and resulting in the conscious perception of these letters. Subsequent cognitive processing results in understanding of the content. As you continue reading, regions of the cerebral cortex in the frontal lobe plan how to move the eyes to follow the lines of text. The output from the cortex causes activity in motor neurons in the brain stem that cause movement of the extraocular muscles through the third, fourth, and sixth cranial nerves. This example also includes sensory input (the retinal projection to the thalamus), central processing (the thalamus and subsequent cortical activity), and motor output (activation of neurons in the brain stem that lead to coordinated contraction of extraocular muscles).

## 14.1 Sensory Perception

### LEARNING OBJECTIVES

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

- Describe different types of sensory receptors
- Describe the structures responsible for the special senses of taste, smell, hearing, balance, and vision
- Distinguish how different tastes are transduced
- Describe the means of mechanoreception for hearing and balance
- List the supporting structures around the eye and describe the structure of the eyeball
- Describe the processes of phototransduction

A major role of sensory receptors is to help us learn about the environment around us, or about the state of our internal environment. Stimuli from varying sources, and of different types, are received and changed into the electrochemical signals of the nervous system. This occurs when a stimulus changes the cell membrane potential of a sensory neuron. The stimulus causes the sensory cell to produce an action potential that is relayed into the central nervous system (CNS), where it is integrated with other sensory information—or sometimes higher cognitive functions—to become a conscious perception of that stimulus. The central integration may then lead to a motor response.

Describing sensory function with the term sensation or perception is a deliberate distinction. Sensation is the activation of sensory receptor cells at the level of the stimulus. Perception is the central processing of sensory stimuli into a meaningful pattern. Perception is dependent on sensation, but not all sensations are perceived. Receptors are the cells or structures that detect sensations. A receptor cell is changed directly by a stimulus. A transmembrane protein receptor is a protein in the cell membrane that mediates a physiological change in a neuron, most often through the opening of ion channels or changes in the cell signaling processes. Transmembrane receptors are activated by chemicals called ligands. For example, a molecule in food can serve as a ligand for taste receptors. Other transmembrane proteins, which are not accurately called receptors, are sensitive to mechanical or thermal changes. Physical changes in these proteins increase ion flow across the membrane, and can generate an action potential or a graded potential in the sensory neurons.

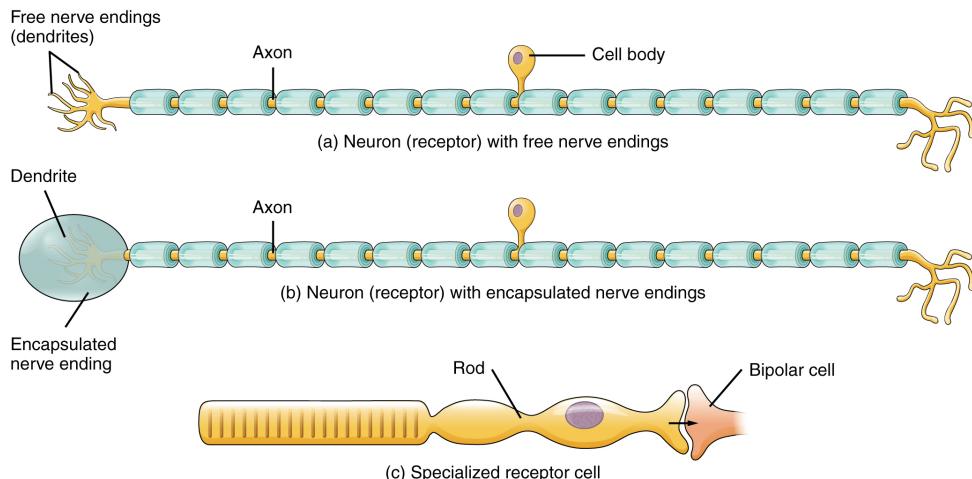
### Sensory Receptors

Stimuli in the environment activate specialized receptor cells in the peripheral nervous system. Different types of stimuli are sensed by different types of receptor cells. Receptor cells can be classified into types on the basis of three different criteria: cell type, position, and function. Receptors can be classified structurally on the basis of cell type and their position in relation to stimuli they sense. They can also be classified functionally on the basis of the **transduction** of stimuli, or how the mechanical stimulus, light, or chemical changed the cell membrane potential.

### Structural Receptor Types

The cells that interpret information about the environment can be either (1) a neuron that has a **free nerve ending**,

with dendrites embedded in tissue that would receive a sensation; (2) a neuron that has an **encapsulated ending** in which the sensory nerve endings are encapsulated in connective tissue that enhances their sensitivity; or (3) a specialized **receptor cell**, which has distinct structural components that interpret a specific type of stimulus (Figure 14.2). The pain and temperature receptors in the dermis of the skin are examples of neurons that have free nerve endings. Also located in the dermis of the skin are lamellated corpuscles, neurons with encapsulated nerve endings that respond to pressure and touch. The cells in the retina that respond to light stimuli are an example of a specialized receptor, a **photoreceptor**.



**FIGURE 14.2 Receptor Classification by Cell Type** Receptor cell types can be classified on the basis of their structure. Sensory neurons can have either (a) free nerve endings or (b) encapsulated endings. Photoreceptors in the eyes, such as rod cells, are examples of (c) specialized receptor cells. These cells release neurotransmitters onto a bipolar cell, which then synapses with the optic nerve neurons.

Another way that receptors can be classified is based on their location relative to the stimuli. An **exteroceptor** is a receptor that is located near a stimulus in the external environment, such as the somatosensory receptors that are located in the skin. An **interoceptor** is one that interprets stimuli from internal organs and tissues, such as the receptors that sense the increase in blood pressure in the aorta or carotid sinus. Finally, a **proprioceptor** is a receptor located near a moving part of the body, such as a muscle, that interprets the positions of the tissues as they move.

### Functional Receptor Types

A third classification of receptors is by how the receptor transduces stimuli into membrane potential changes. Stimuli are of three general types. Some stimuli are ions and macromolecules that affect transmembrane receptor proteins when these chemicals diffuse across the cell membrane. Some stimuli are physical variations in the environment that affect receptor cell membrane potentials. Other stimuli include the electromagnetic radiation from visible light. For humans, the only electromagnetic energy that is perceived by our eyes is visible light. Some other organisms have receptors that humans lack, such as the heat sensors of snakes, the ultraviolet light sensors of bees, or magnetic receptors in migratory birds.

Receptor cells can be further categorized on the basis of the type of stimuli they transduce. Chemical stimuli can be interpreted by a **chemoreceptor** that interprets chemical stimuli, such as an object's taste or smell. **Osmoreceptors** respond to solute concentrations of body fluids. Additionally, pain is primarily a chemical sense that interprets the presence of chemicals from tissue damage, or similar intense stimuli, through a **nociceptor**. Physical stimuli, such as pressure and vibration, as well as the sensation of sound and body position (balance), are interpreted through a **mechanoreceptor**. Another physical stimulus that has its own type of receptor is temperature, which is sensed through a **thermoreceptor** that is either sensitive to temperatures above (heat) or below (cold) normal body temperature.

### Sensory Modalities

Ask anyone what the senses are, and they are likely to list the five major senses—taste, smell, touch, hearing, and sight. However, these are not all of the senses. The most obvious omission from this list is balance. Also, what is referred to simply as touch can be further subdivided into pressure, vibration, stretch, and hair-follicle position, on

the basis of the type of mechanoreceptors that perceive these touch sensations. Other overlooked senses include temperature perception by thermoreceptors and pain perception by nociceptors.

Within the realm of physiology, senses can be classified as either general or specific. A **general sense** is one that is distributed throughout the body and has receptor cells within the structures of other organs. Mechanoreceptors in the skin, muscles, or the walls of blood vessels are examples of this type. General senses often contribute to the sense of touch, as described above, or to **proprioception** (body movement) and **kinesthesia** (body movement), or to a **visceral sense**, which is most important to autonomic functions. A **special sense** is one that has a specific organ devoted to it, namely the eye, inner ear, tongue, or nose.

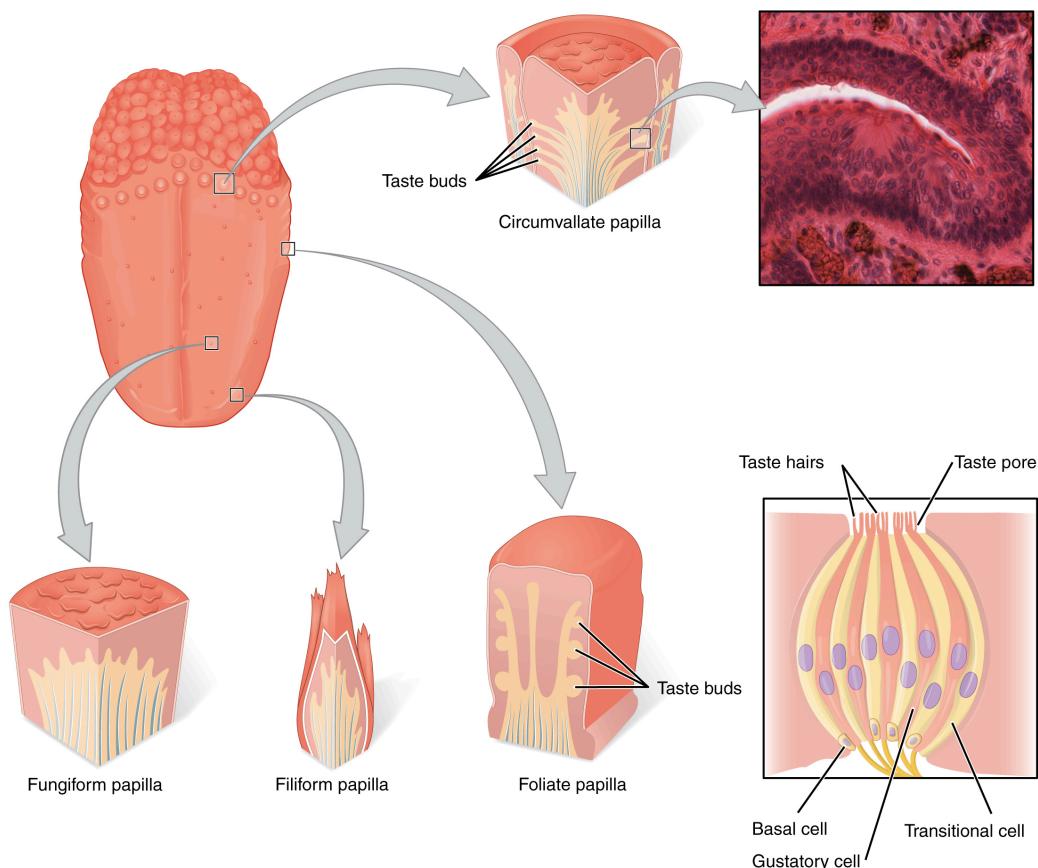
Each of the senses is referred to as a **sensory modality**. Modality refers to the way that information is encoded, which is similar to the idea of transduction. The main sensory modalities can be described on the basis of how each is transduced. The chemical senses are taste and smell. The general sense that is usually referred to as touch includes chemical sensation in the form of nociception, or pain. Pressure, vibration, muscle stretch, and the movement of hair by an external stimulus, are all sensed by mechanoreceptors. Hearing and balance are also sensed by mechanoreceptors. Finally, vision involves the activation of photoreceptors.

Listing all the different sensory modalities, which can number as many as 17, involves separating the five major senses into more specific categories, or **submodalities**, of the larger sense. An individual sensory modality represents the sensation of a specific type of stimulus. For example, the general sense of touch, which is known as **somatosensation**, can be separated into light pressure, deep pressure, vibration, itch, pain, temperature, or hair movement.

#### Gustation (Taste)

Only a few recognized submodalities exist within the sense of taste, or **gustation**. Until recently, only four tastes were recognized: sweet, salty, sour, and bitter. Research at the turn of the 20th century led to recognition of the fifth taste, umami, during the mid-1980s. **Umami** is a Japanese word that means “delicious taste,” and is often translated to mean savory. Very recent research has suggested that there may also be a sixth taste for fats, or lipids.

Gustation is the special sense associated with the tongue. The surface of the tongue, along with the rest of the oral cavity, is lined by a stratified squamous epithelium. Raised bumps called **papillae** (singular = papilla) contain the structures for gustatory transduction. There are four types of papillae, based on their appearance ([Figure 14.3](#)): circumvallate, foliate, filiform, and fungiform. Within the structure of the papillae are **taste buds** that contain specialized **gustatory receptor cells** for the transduction of taste stimuli. These receptor cells are sensitive to the chemicals contained within foods that are ingested, and they release neurotransmitters based on the amount of the chemical in the food. Neurotransmitters from the gustatory cells can activate sensory neurons in the facial, glossopharyngeal, and vagus cranial nerves.



**FIGURE 14.3 The Tongue** The tongue is covered with small bumps, called papillae, which contain taste buds that are sensitive to chemicals in ingested food or drink. Different types of papillae are found in different regions of the tongue. The taste buds contain specialized gustatory receptor cells that respond to chemical stimuli dissolved in the saliva. These receptor cells activate sensory neurons that are part of the facial and glossopharyngeal nerves. LM  $\times 1600$ . (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Salty taste is simply the perception of sodium ions ( $\text{Na}^+$ ) in the saliva. When you eat something salty, the salt crystals dissociate into the component ions  $\text{Na}^+$  and  $\text{Cl}^-$ , which dissolve into the saliva in your mouth. The  $\text{Na}^+$  concentration becomes high outside the gustatory cells, creating a strong concentration gradient that drives the diffusion of the ion into the cells. The entry of  $\text{Na}^+$  into these cells results in the depolarization of the cell membrane and the generation of a receptor potential.

Sour taste is the perception of  $\text{H}^+$  concentration. Just as with sodium ions in salty flavors, these hydrogen ions enter the cell and trigger depolarization. Sour flavors are, essentially, the perception of acids in our food. Increasing hydrogen ion concentrations in the saliva (lowering saliva pH) triggers progressively stronger graded potentials in the gustatory cells. For example, orange juice—which contains citric acid—will taste sour because it has a pH value of approximately 3. Of course, it is often sweetened so that the sour taste is masked.

The first two tastes (salty and sour) are triggered by the cations  $\text{Na}^+$  and  $\text{H}^+$ . The other tastes result from food molecules binding to a G protein-coupled receptor. A G protein signal transduction system ultimately leads to depolarization of the gustatory cell. The sweet taste is the sensitivity of gustatory cells to the presence of glucose dissolved in the saliva. Other monosaccharides such as fructose, or artificial sweeteners such as aspartame (NutraSweet™), saccharine, or sucralose (Splenda™) also activate the sweet receptors. The affinity for each of these molecules varies, and some will taste sweeter than glucose because they bind to the G protein-coupled receptor differently.

Bitter taste is similar to sweet in that food molecules bind to G protein-coupled receptors. However, there are a number of different ways in which this can happen because there are a large diversity of bitter-tasting molecules. Some bitter molecules depolarize gustatory cells, whereas others hyperpolarize gustatory cells. Likewise, some bitter molecules increase G protein activation within the gustatory cells, whereas other bitter molecules decrease G

protein activation. The specific response depends on which molecule is binding to the receptor.

One major group of bitter-tasting molecules are alkaloids. **Alkaloids** are nitrogen containing molecules that are commonly found in bitter-tasting plant products, such as coffee, hops (in beer), tannins (in wine), tea, and aspirin. By containing toxic alkaloids, the plant is less susceptible to microbe infection and less attractive to herbivores.

Therefore, the function of bitter taste may primarily be related to stimulating the gag reflex to avoid ingesting poisons. Because of this, many bitter foods that are normally ingested are often combined with a sweet component to make them more palatable (cream and sugar in coffee, for example). The highest concentration of bitter receptors appear to be in the posterior tongue, where a gag reflex could still spit out poisonous food.

The taste known as umami is often referred to as the savory taste. Like sweet and bitter, it is based on the activation of G protein–coupled receptors by a specific molecule. The molecule that activates this receptor is the amino acid L-glutamate. Therefore, the umami flavor is often perceived while eating protein-rich foods. Not surprisingly, dishes that contain meat are often described as savory.

Once the gustatory cells are activated by the taste molecules, they release neurotransmitters onto the dendrites of sensory neurons. These neurons are part of the facial and glossopharyngeal cranial nerves, as well as a component within the vagus nerve dedicated to the gag reflex. The facial nerve connects to taste buds in the anterior third of the tongue. The glossopharyngeal nerve connects to taste buds in the posterior two thirds of the tongue. The vagus nerve connects to taste buds in the extreme posterior of the tongue, verging on the pharynx, which are more sensitive to noxious stimuli such as bitterness.

## INTERACTIVE LINK

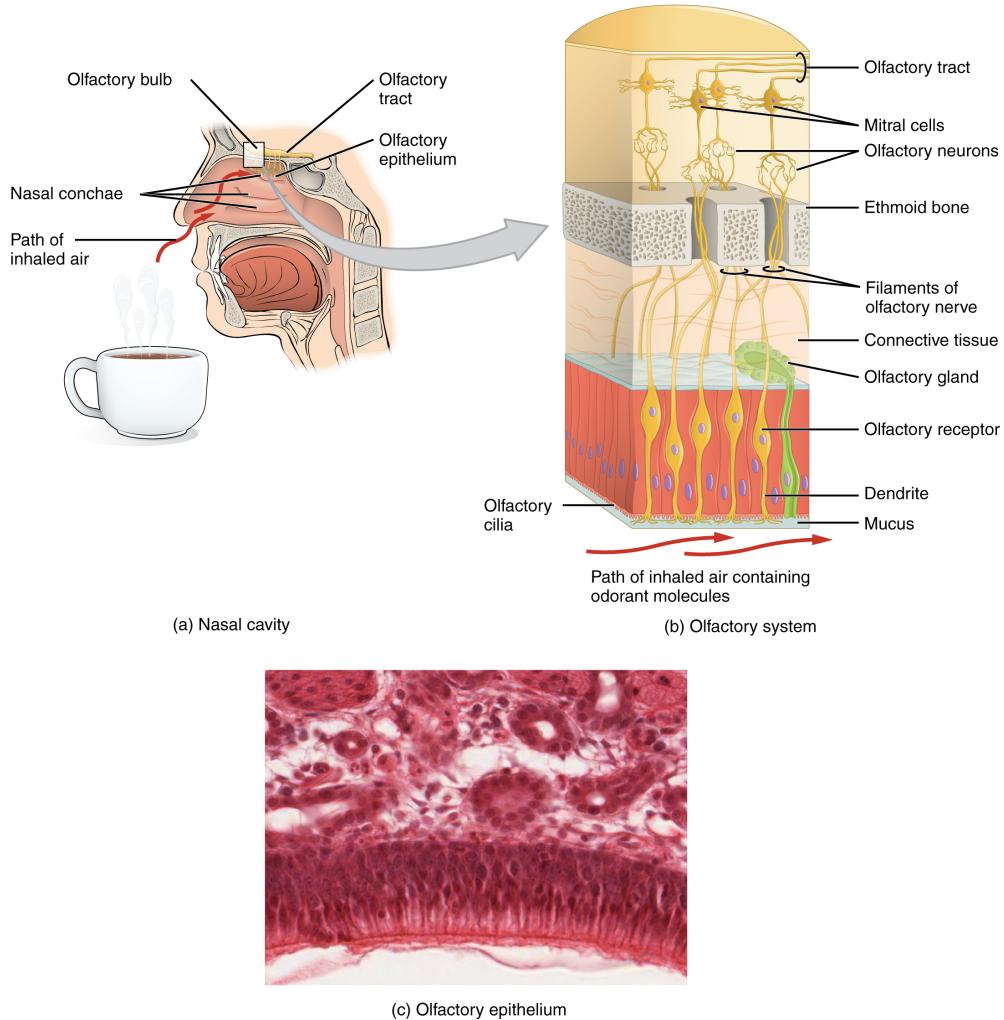
Watch this [video \(<http://openstax.org/l/DanielleReed>\)](http://openstax.org/l/DanielleReed) to learn about Dr. Danielle Reed of the Monell Chemical Senses Center in Philadelphia, Pennsylvania, who became interested in science at an early age because of her sensory experiences. She recognized that her sense of taste was unique compared with other people she knew. Now, she studies the genetic differences between people and their sensitivities to taste stimuli. In the video, there is a brief image of a person sticking out their tongue, which has been covered with a colored dye. This is how Dr. Reed is able to visualize and count papillae on the surface of the tongue. People fall into two groups known as “tasters” and “non-tasters” based on the density of papillae on their tongue, which also indicates the number of taste buds. Non-tasters can taste food, but they are not as sensitive to certain tastes, such as bitterness. Dr. Reed discovered that she is a non-taster, which explains why she perceived bitterness differently than other people she knew. Are you very sensitive to tastes? Can you see any similarities among the members of your family?

### Olfaction (Smell)

Like taste, the sense of smell, or **olfaction**, is also responsive to chemical stimuli. The olfactory receptor neurons are located in a small region within the superior nasal cavity ([Figure 14.4](#)). This region is referred to as the **olfactory epithelium** and contains bipolar sensory neurons. Each **olfactory sensory neuron** has dendrites that extend from the apical surface of the epithelium into the mucus lining the cavity. As airborne molecules are inhaled through the nose, they pass over the olfactory epithelial region and dissolve into the mucus. These **odorant molecules** bind to proteins that keep them dissolved in the mucus and help transport them to the olfactory dendrites. The odorant–protein complex binds to a receptor protein within the cell membrane of an olfactory dendrite. These receptors are G protein–coupled, and will produce a graded membrane potential in the olfactory neurons.

The axon of an olfactory neuron extends from the basal surface of the epithelium, through an olfactory foramen in the cribriform plate of the ethmoid bone, and into the brain. The group of axons called the olfactory tract connect to the **olfactory bulb** on the ventral surface of the frontal lobe. From there, the axons split to travel to several brain regions. Some travel to the cerebrum, specifically to the primary olfactory cortex that is located in the inferior and medial areas of the temporal lobe. Others project to structures within the limbic system and hypothalamus, where smells become associated with long-term memory and emotional responses. This is how certain smells trigger emotional memories, such as the smell of food associated with one’s birthplace. Smell is the one sensory modality that does not synapse in the thalamus before connecting to the cerebral cortex. This intimate connection between the olfactory system and the cerebral cortex is one reason why smell can be a potent trigger of memories and emotion.

The nasal epithelium, including the olfactory cells, can be harmed by airborne toxic chemicals. Therefore, the olfactory neurons are regularly replaced within the nasal epithelium, after which the axons of the new neurons must find their appropriate connections in the olfactory bulb. These new axons grow along the axons that are already in place in the cranial nerve.



**FIGURE 14.4 The Olfactory System** (a) The olfactory system begins in the peripheral structures of the nasal cavity. (b) The olfactory receptor neurons are within the olfactory epithelium. (c) Axons of the olfactory receptor neurons project through the cribriform plate of the ethmoid bone and synapse with the neurons of the olfactory bulb (tissue source: simian). LM  $\times 812$ . (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

### Disorders of the...

#### Olfactory System: Anosmia

Blunt force trauma to the face, such as that common in many car accidents, can lead to the loss of the olfactory nerve, and subsequently, loss of the sense of smell. This condition is known as **anosmia**. When the frontal lobe of the brain moves relative to the ethmoid bone, the olfactory tract axons may be sheared apart. Professional fighters often experience anosmia because of repeated trauma to face and head. In addition, certain pharmaceuticals, such as antibiotics, can cause anosmia by killing all the olfactory neurons at once. If no axons are in place within the olfactory nerve, then the axons from newly formed olfactory neurons have no guide to lead them to their connections within the olfactory bulb. There are temporary causes of anosmia, as well, such as those caused by inflammatory responses related to respiratory infections or allergies.

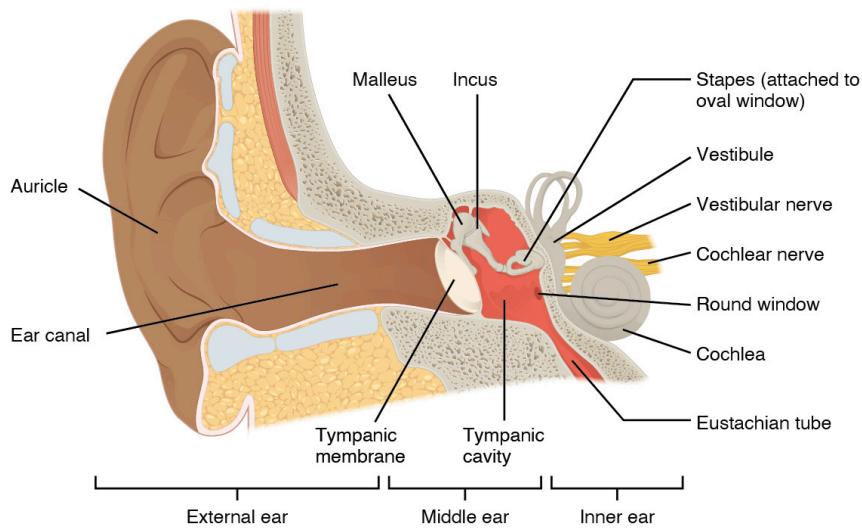
Loss of the sense of smell can result in food tasting bland. A person with an impaired sense of smell may require additional spice and seasoning levels for food to be tasted. Anosmia may also be related to some presentations

of mild depression, because the loss of enjoyment of food may lead to a general sense of despair.

The ability of olfactory neurons to replace themselves decreases with age, leading to age-related anosmia. This explains why some elderly people salt their food more than younger people do. However, this increased sodium intake can increase blood volume and blood pressure, increasing the risk of cardiovascular diseases in the elderly.

### Audition (Hearing)

Hearing, or **audition**, is the transduction of sound waves into a neural signal that is made possible by the structures of the ear ([Figure 14.5](#)). The large, fleshy structure on the lateral aspect of the head is known as the **auricle**. Some sources will also refer to this structure as the pinna, though that term is more appropriate for a structure that can be moved, such as the external ear of a cat. The C-shaped curves of the auricle direct sound waves toward the auditory canal. The canal enters the skull through the external auditory meatus of the temporal bone. At the end of the auditory canal is the **tympanic membrane**, or ear drum, which vibrates after it is struck by sound waves. The auricle, ear canal, and tympanic membrane are often referred to as the **external ear**. The **middle ear** consists of a space spanned by three small bones called the **ossicles**. The three ossicles are the **malleus**, **incus**, and **stapes**, which are Latin names that roughly translate to hammer, anvil, and stirrup. The malleus is attached to the tympanic membrane and articulates with the incus. The incus, in turn, articulates with the stapes. The stapes is then attached to the **inner ear**, where the sound waves will be transduced into a neural signal. The middle ear is connected to the pharynx through the Eustachian tube, which helps equilibrate air pressure across the tympanic membrane. The tube is normally closed but will pop open when the muscles of the pharynx contract during swallowing or yawning.

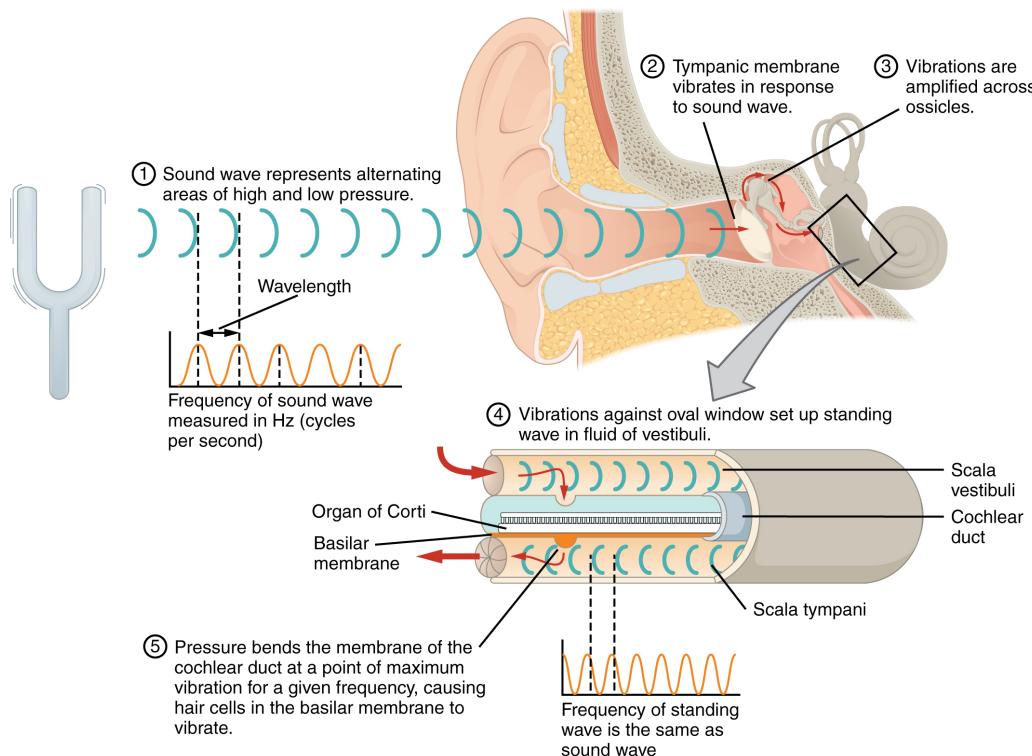


**FIGURE 14.5 Structures of the Ear** The external ear contains the auricle, ear canal, and tympanic membrane. The middle ear contains the ossicles and is connected to the pharynx by the Eustachian tube. The inner ear contains the cochlea and vestibule, which are responsible for audition and equilibrium, respectively.

The inner ear is often described as a bony labyrinth, as it is composed of a series of canals embedded within the temporal bone. It has two separate regions, the **cochlea** and the **vestibule**, which are responsible for hearing and balance, respectively. The neural signals from these two regions are relayed to the brain stem through separate fiber bundles. However, these two distinct bundles travel together from the inner ear to the brain stem as the **vestibulocochlear nerve**. Sound is transduced into neural signals within the cochlear region of the inner ear, which contains the sensory neurons of the **spiral ganglia**. These ganglia are located within the spiral-shaped cochlea of the inner ear. The cochlea is attached to the stapes through the **oval window**.

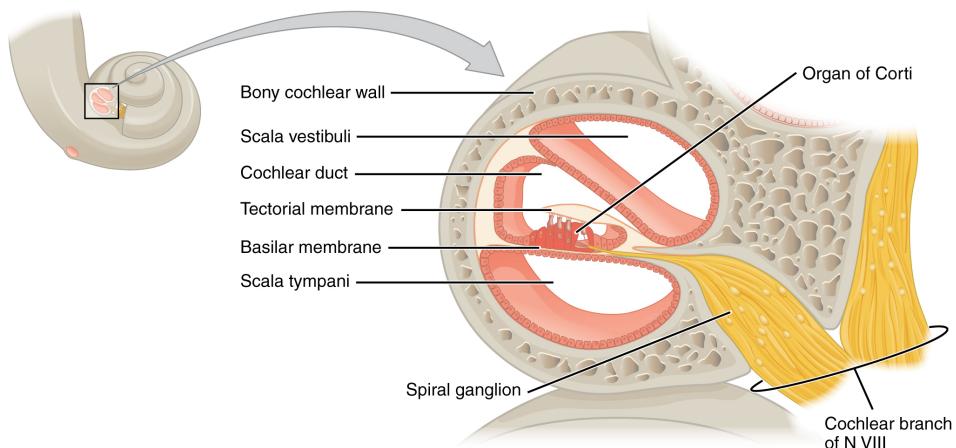
The oval window is located at the beginning of a fluid-filled tube within the cochlea called the **scala vestibuli**. The scala vestibuli extends from the oval window, travelling above the **cochlear duct**, which is the central cavity of the cochlea that contains the sound-transducing neurons. At the uppermost tip of the cochlea, the scala vestibuli curves over the top of the cochlear duct. The fluid-filled tube, now called the **scala tympani**, returns to the base of the cochlea, this time travelling under the cochlear duct. The scala tympani ends at the **round window**, which is

covered by a membrane that contains the fluid within the scala. As vibrations of the ossicles travel through the oval window, the fluid of the scala vestibuli and scala tympani moves in a wave-like motion. The frequency of the fluid waves match the frequencies of the sound waves (Figure 14.6). The membrane covering the round window will bulge out or pucker in with the movement of the fluid within the scala tympani.



**FIGURE 14.6 Transmission of Sound Waves to Cochlea** A sound wave causes the tympanic membrane to vibrate. This vibration is amplified as it moves across the malleus, incus, and stapes. The amplified vibration is picked up by the oval window causing pressure waves in the fluid of the scala vestibuli and scala tympani. The complexity of the pressure waves is determined by the changes in amplitude and frequency of the sound waves entering the ear.

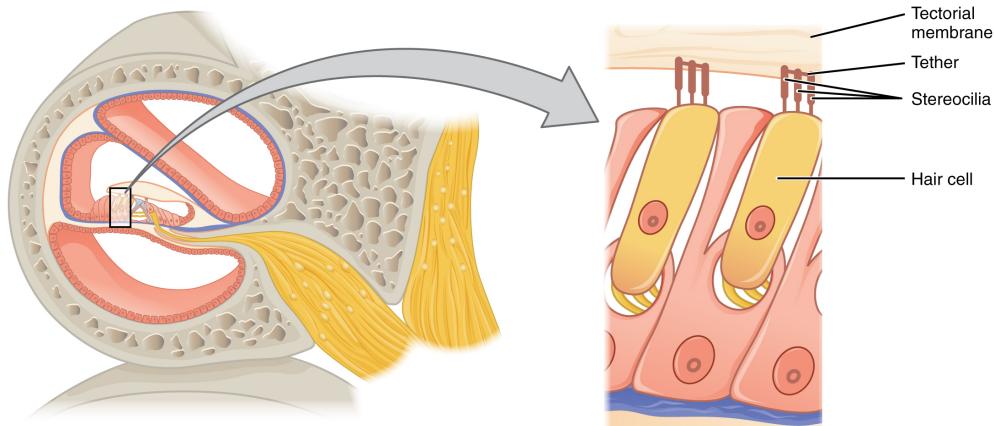
A cross-sectional view of the cochlea shows that the scala vestibuli and scala tympani run along both sides of the cochlear duct (Figure 14.7). The cochlear duct contains several **organs of Corti**, which transduce the wave motion of the two scala into neural signals. The organs of Corti lie on top of the **basilar membrane**, which is the side of the cochlear duct located between the organs of Corti and the scala tympani. As the fluid waves move through the scala vestibuli and scala tympani, the basilar membrane moves at a specific spot, depending on the frequency of the waves. Higher frequency waves move the region of the basilar membrane that is close to the base of the cochlea. Lower frequency waves move the region of the basilar membrane that is near the tip of the cochlea.



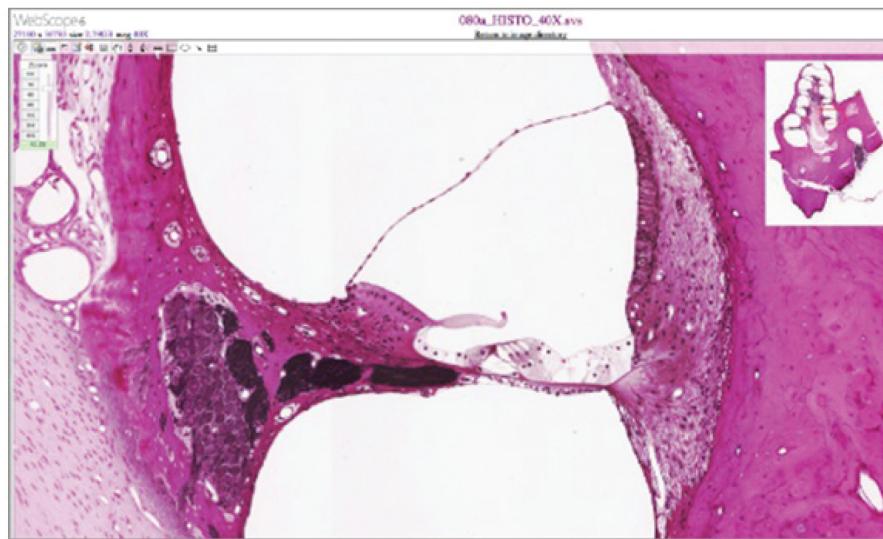
**FIGURE 14.7 Cross Section of the Cochlea** The three major spaces within the cochlea are highlighted. The scala tympani and scala

vestibuli lie on either side of the cochlear duct. The organ of Corti, containing the mechanoreceptor hair cells, is adjacent to the scala tympani, where it sits atop the basilar membrane.

The organs of Corti contain **hair cells**, which are named for the hair-like **stereocilia** extending from the cell's apical surfaces ([Figure 14.8](#)). The stereocilia are an array of microvilli-like structures arranged from tallest to shortest. Protein fibers tether adjacent hairs together within each array, such that the array will bend in response to movements of the basilar membrane. The stereocilia extend up from the hair cells to the overlying **tectorial membrane**, which is attached medially to the organ of Corti. When the pressure waves from the scala move the basilar membrane, the tectorial membrane slides across the stereocilia. This bends the stereocilia either toward or away from the tallest member of each array. When the stereocilia bend toward the tallest member of their array, tension in the protein tethers opens ion channels in the hair cell membrane. This will depolarize the hair cell membrane, triggering nerve impulses that travel down the afferent nerve fibers attached to the hair cells. When the stereocilia bend toward the shortest member of their array, the tension on the tethers slackens and the ion channels close. When no sound is present, and the stereocilia are standing straight, a small amount of tension still exists on the tethers, keeping the membrane potential of the hair cell slightly depolarized.



**FIGURE 14.8 Hair Cell** The hair cell is a mechanoreceptor with an array of stereocilia emerging from its apical surface. The stereocilia are tethered together by proteins that open ion channels when the array is bent toward the tallest member of their array, and closed when the array is bent toward the shortest member of their array.



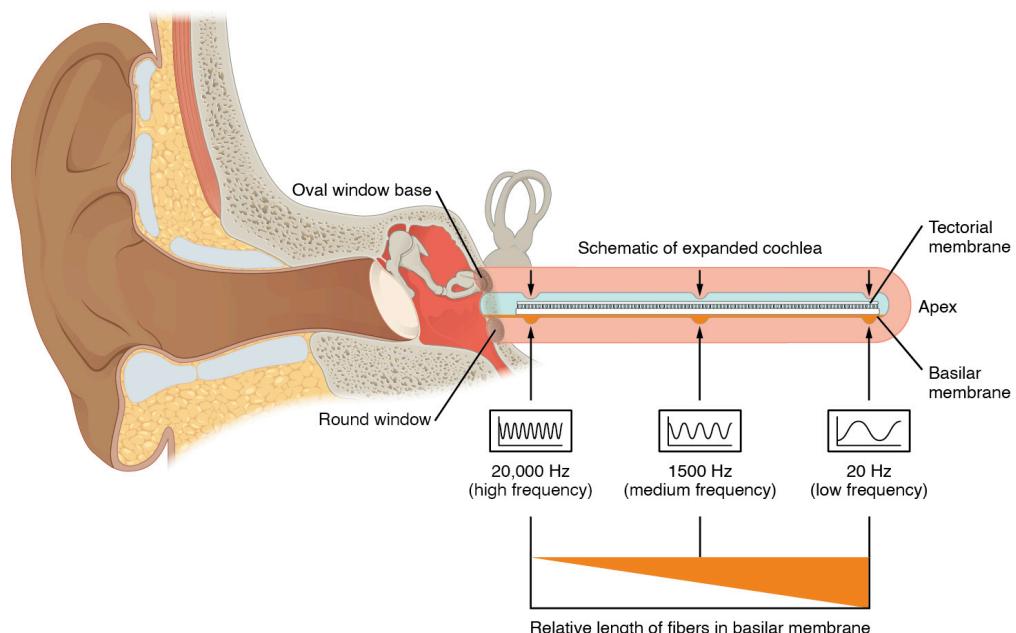
**FIGURE 14.9 Cochlea and Organ of Corti** LM × 412. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

### INTERACTIVE LINK

View the [University of Michigan WebScope](http://openstax.org/l/cochleaMG) (<http://openstax.org/l/cochleaMG>) to explore the tissue sample in greater detail. The basilar membrane is the thin membrane that extends from the central core of the cochlea to the edge.

What is anchored to this membrane so that they can be activated by movement of the fluids within the cochlea?

As stated above, a given region of the basilar membrane will only move if the incoming sound is at a specific frequency. Because the tectorial membrane only moves where the basilar membrane moves, the hair cells in this region will also only respond to sounds of this specific frequency. Therefore, as the frequency of a sound changes, different hair cells are activated all along the basilar membrane. The cochlea encodes auditory stimuli for frequencies between 20 and 20,000 Hz, which is the range of sound that human ears can detect. The unit of Hertz measures the frequency of sound waves in terms of cycles produced per second. Frequencies as low as 20 Hz are detected by hair cells at the apex, or tip, of the cochlea. Frequencies in the higher ranges of 20 KHz are encoded by hair cells at the base of the cochlea, close to the round and oval windows (Figure 14.10). Most auditory stimuli contain a mixture of sounds at a variety of frequencies and intensities (represented by the amplitude of the sound wave). The hair cells along the length of the cochlear duct, which are each sensitive to a particular frequency, allow the cochlea to separate auditory stimuli by frequency, just as a prism separates visible light into its component colors.



**FIGURE 14.10 Frequency Coding in the Cochlea** The standing sound wave generated in the cochlea by the movement of the oval window deflects the basilar membrane on the basis of the frequency of sound. Therefore, hair cells at the base of the cochlea are activated only by high frequencies, whereas those at the apex of the cochlea are activated only by low frequencies.

### INTERACTIVE LINK

Watch this [video](http://openstax.org/l/ear1) (<http://openstax.org/l/ear1>) to learn more about how the structures of the ear convert sound waves into a neural signal by moving the “hairs,” or stereocilia, of the cochlear duct. Specific locations along the length of the duct encode specific frequencies, or pitches. The brain interprets the meaning of the sounds we hear as music, speech, noise, etc. Which ear structures are responsible for the amplification and transfer of sound from the external ear to the inner ear?

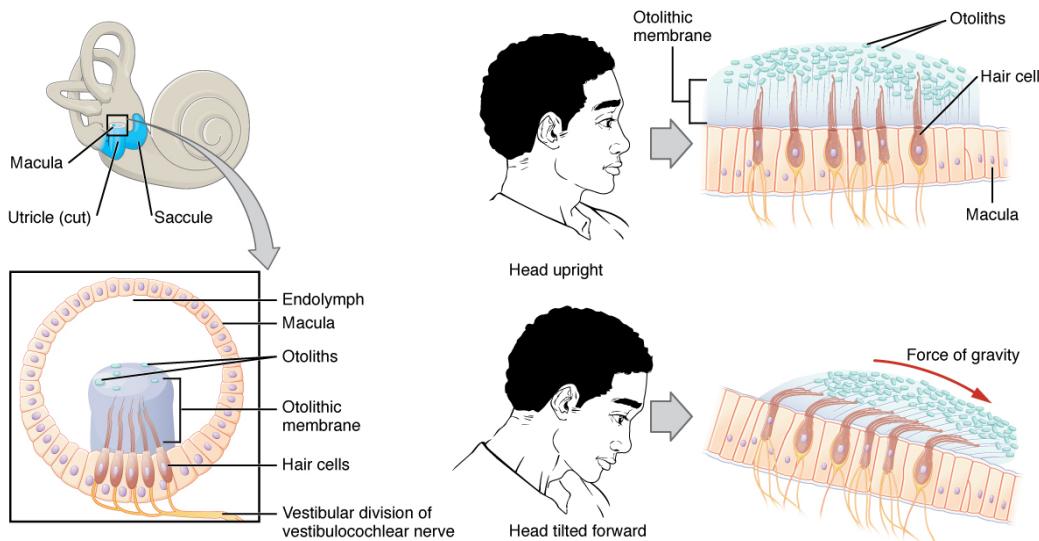
### INTERACTIVE LINK

Watch this [animation](http://openstax.org/l/ear2) (<http://openstax.org/l/ear2>) to learn more about the inner ear and to see the cochlea unroll, with the base at the back of the image and the apex at the front. Specific wavelengths of sound cause specific regions of the basilar membrane to vibrate, much like the keys of a piano produce sound at different frequencies. Based on the animation, where do frequencies—from high to low pitches—cause activity in the hair cells within the cochlear duct?

### Equilibrium (Balance)

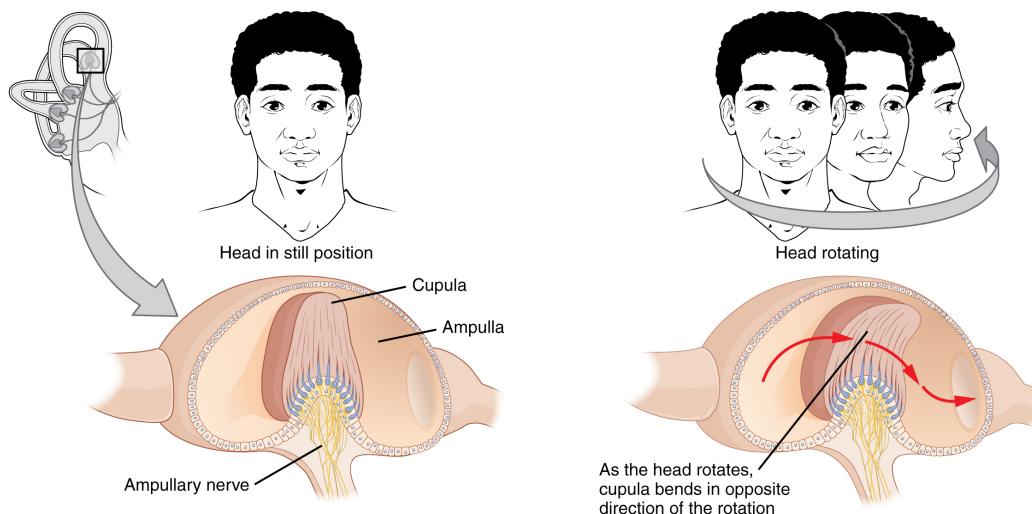
Along with audition, the inner ear is responsible for encoding information about **equilibrium**, the sense of balance. A similar mechanoreceptor—a hair cell with stereocilia—senses head position, head movement, and whether our bodies are in motion. These cells are located within the vestibule of the inner ear. Head position is sensed by the **utricle** and **saccule**, whereas head movement is sensed by the **semicircular canals**. The neural signals generated in the **vestibular ganglion** are transmitted through the vestibulocochlear nerve to the brain stem and cerebellum.

The utricle and saccule are both largely composed of **macula** tissue (plural = maculae). The macula is composed of hair cells surrounded by support cells. The stereocilia of the hair cells extend into a viscous gel called the **otolithic membrane** ([Figure 14.11](#)). On top of the otolithic membrane is a layer of calcium carbonate crystals, called **otoliths**. The otoliths essentially make the otolithic membrane top-heavy. The otolithic membrane moves separately from the macula in response to head movements. Tilting the head causes the otolithic membrane to slide over the macula in the direction of gravity. The moving otolithic membrane, in turn, bends the stereocilia, causing some hair cells to depolarize as others hyperpolarize. The exact position of the head is interpreted by the brain based on the pattern of hair-cell depolarization.



**FIGURE 14.11** Linear Acceleration Coding by Maculae The maculae are specialized for sensing linear acceleration, such as when gravity acts on the tilting head, or if the head starts moving in a straight line. The difference in inertia between the hair cell stereocilia and the otolithic membrane in which they are embedded leads to a shearing force that causes the stereocilia to bend in the direction of that linear acceleration.

The semicircular canals are three ring-like extensions of the vestibule. One is oriented in the horizontal plane, whereas the other two are oriented in the vertical plane. The anterior and posterior vertical canals are oriented at approximately 45 degrees relative to the sagittal plane ([Figure 14.12](#)). The base of each semicircular canal, where it meets with the vestibule, connects to an enlarged region known as the **ampulla**. The ampulla contains the hair cells that respond to rotational movement, such as turning the head while saying “no.” The stereocilia of these hair cells extend into the **cupula**, a membrane that attaches to the top of the ampulla. As the head rotates in a plane parallel to the semicircular canal, the fluid lags, deflecting the cupula in the direction opposite to the head movement. The semicircular canals contain several ampullae, with some oriented horizontally and others oriented vertically. By comparing the relative movements of both the horizontal and vertical ampullae, the vestibular system can detect the direction of most head movements within three-dimensional (3-D) space.



**FIGURE 14.12 Rotational Coding by Semicircular Canals** Rotational movement of the head is encoded by the hair cells in the base of the semicircular canals. As one of the canals moves in an arc with the head, the internal fluid moves in the opposite direction, causing the cupula and stereocilia to bend. The movement of two canals within a plane results in information about the direction in which the head is moving, and activation of all six canals can give a very precise indication of head movement in three dimensions.

### Somatosensation (Touch)

Somatosensation is considered a general sense, as opposed to the special senses discussed in this section. Somatosensation is the group of sensory modalities that are associated with touch, proprioception, and interoception. These modalities include pressure, vibration, light touch, tickle, itch, temperature, pain, proprioception, and kinesthesia. This means that its receptors are not associated with a specialized organ, but are instead spread throughout the body in a variety of organs. Many of the somatosensory receptors are located in the skin, but receptors are also found in muscles, tendons, joint capsules, ligaments, and in the walls of visceral organs.

Two types of somatosensory signals that are transduced by free nerve endings are pain and temperature. These two modalities use thermoreceptors and nociceptors to transduce temperature and pain stimuli, respectively. Temperature receptors are stimulated when local temperatures differ from body temperature. Some thermoreceptors are sensitive to just cold and others to just heat. Nociception is the sensation of potentially damaging stimuli. Mechanical, chemical, or thermal stimuli beyond a set threshold will elicit painful sensations. Stressed or damaged tissues release chemicals that activate receptor proteins in the nociceptors. For example, the sensation of heat associated with spicy foods involves **capsaicin**, the active molecule in hot peppers. Capsaicin molecules bind to a transmembrane ion channel in nociceptors that is sensitive to temperatures above 37°C. The dynamics of capsaicin binding with this transmembrane ion channel is unusual in that the molecule remains bound for a long time. Because of this, it will decrease the ability of other stimuli to elicit pain sensations through the activated nociceptor. For this reason, capsaicin can be used as a topical analgesic, such as in products such as Icy Hot™.

If you drag your finger across a textured surface, the skin of your finger will vibrate. Such low frequency vibrations are sensed by mechanoreceptors called Merkel cells, also known as type I cutaneous mechanoreceptors. Merkel cells are located in the stratum basale of the epidermis. Deep pressure and vibration is transduced by lamellated (Pacinian) corpuscles, which are receptors with encapsulated endings found deep in the dermis, or subcutaneous tissue. Light touch is transduced by the encapsulated endings known as tactile (Meissner) corpuscles. Follicles are also wrapped in a plexus of nerve endings known as the hair follicle plexus. These nerve endings detect the movement of hair at the surface of the skin, such as when an insect may be walking along the skin. Stretching of the skin is transduced by stretch receptors known as bulbous corpuscles. Bulbous corpuscles are also known as Ruffini corpuscles, or type II cutaneous mechanoreceptors.

Other somatosensory receptors are found in the joints and muscles. Stretch receptors monitor the stretching of tendons, muscles, and the components of joints. For example, have you ever stretched your muscles before or after exercise and noticed that you can only stretch so far before your muscles spasm back to a less stretched state? This spasm is a reflex that is initiated by stretch receptors to avoid muscle tearing. Such stretch receptors can also prevent over-contraction of a muscle. In skeletal muscle tissue, these stretch receptors are called muscle spindles.

Golgi tendon organs similarly transduce the stretch levels of tendons. Bulbous corpuscles are also present in joint capsules, where they measure stretch in the components of the skeletal system within the joint. The types of nerve endings, their locations, and the stimuli they transduce are presented in [Table 14.1](#).

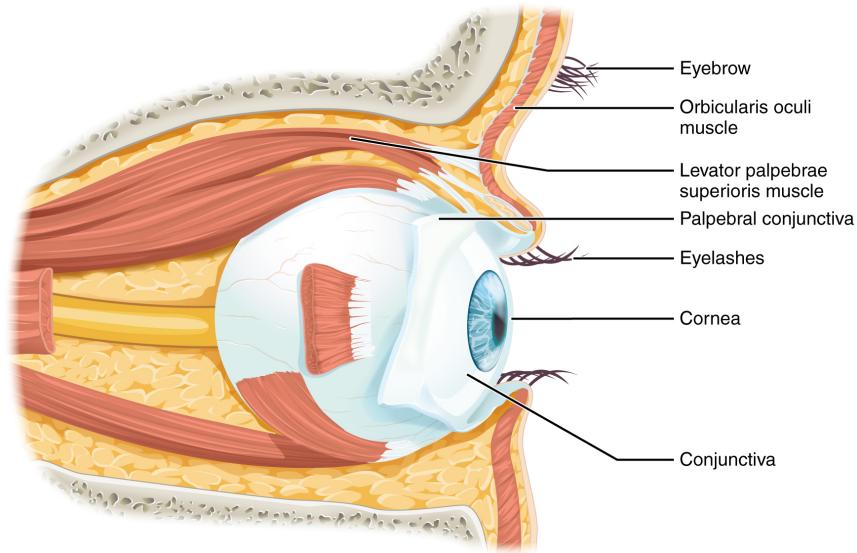
#### Mechanoreceptors of Somatosensation

Name	Historical (eponymous) name	Location(s)	Stimuli
Free nerve endings	*	Dermis, cornea, tongue, joint capsules, visceral organs	Pain, temperature, mechanical deformation
Mechanoreceptors	Merkel's discs	Epidermal–dermal junction, mucosal membranes	Low frequency vibration (5–15 Hz)
Bulbous corpuscle	Ruffini's corpuscle	Dermis, joint capsules	Stretch
Tactile corpuscle	Meissner's corpuscle	Papillary dermis, especially in the fingertips and lips	Light touch, vibrations below 50 Hz
Lamellated corpuscle	Pacinian corpuscle	Deep dermis, subcutaneous tissue	Deep pressure, high-frequency vibration (around 250 Hz)
Hair follicle plexus	*	Wrapped around hair follicles in the dermis	Movement of hair
Muscle spindle	*	In line with skeletal muscle fibers	Muscle contraction and stretch
Tendon stretch organ	Golgi tendon organ	In line with tendons	Stretch of tendons

**TABLE 14.1** \*No corresponding eponymous name.

#### Vision

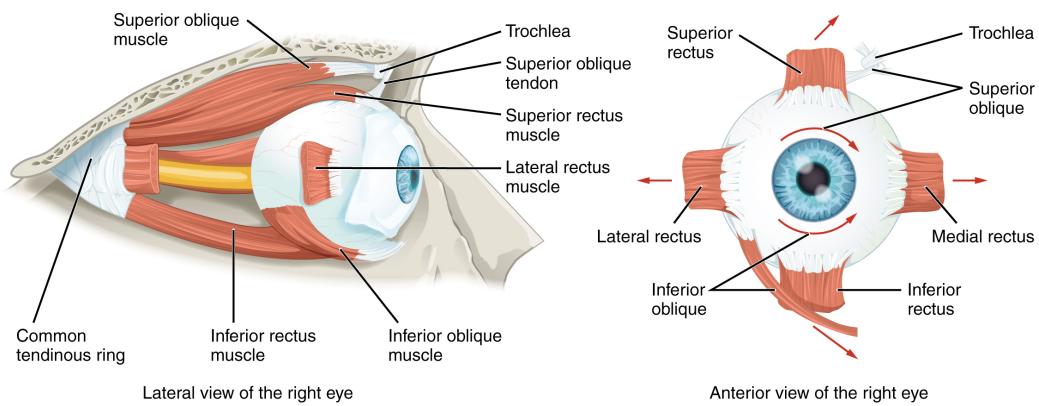
**Vision** is the special sense of sight that is based on the transduction of light stimuli received through the eyes. The eyes are located within either orbit in the skull. The bony orbits surround the eyeballs, protecting them and anchoring the soft tissues of the eye ([Figure 14.13](#)). The eyelids, with lashes at their leading edges, help to protect the eye from abrasions by blocking particles that may land on the surface of the eye. The inner surface of each lid is a thin membrane known as the **palpebral conjunctiva**. The conjunctiva extends over the white areas of the eye (the sclera), connecting the eyelids to the eyeball. Tears are produced by the **lacrimal gland**, located just inside the orbit, superior and lateral to the eyeball. Tears produced by this gland flow through the **lacrimal duct** to the medial corner of the eye, where the tears flow over the conjunctiva, washing away foreign particles.



**FIGURE 14.13 The Eye in the Orbit** The eye is located within the orbit and surrounded by soft tissues that protect and support its function. The orbit is surrounded by cranial bones of the skull.

Movement of the eye within the orbit is accomplished by the contraction of six **extraocular muscles** that originate from the bones of the orbit and insert into the surface of the eyeball (Figure 14.14). Four of the muscles are arranged at the cardinal points around the eye and are named for those locations. They are the **superior rectus**, **medial rectus**, **inferior rectus**, and **lateral rectus**. When each of these muscles contracts, the eye moves toward the contracting muscle. For example, when the superior rectus contracts, the eye rotates to look up. The **superior oblique** originates at the posterior orbit, near the origin of the four rectus muscles. However, the tendon of the oblique muscles threads through a pulley-like piece of cartilage known as the **trochlea**. The tendon inserts obliquely into the superior surface of the eye. The angle of the tendon through the trochlea means that contraction of the superior oblique rotates the eye laterally. The **inferior oblique** muscle originates from the floor of the orbit and inserts into the inferolateral surface of the eye. When it contracts, it laterally rotates the eye, in opposition to the superior oblique. Rotation of the eye by the two oblique muscles is necessary because the eye is not perfectly aligned on the sagittal plane. When the eye looks up or down, the eye must also rotate slightly to compensate for the superior rectus pulling at approximately a 20-degree angle, rather than straight up. The same is true for the inferior rectus, which is compensated by contraction of the inferior oblique. A seventh muscle in the orbit is the **levator palpebrae superioris**, which is responsible for elevating and retracting the upper eyelid, a movement that usually occurs in concert with elevation of the eye by the superior rectus (see Figure 14.13).

The extraocular muscles are innervated by three cranial nerves. The lateral rectus, which causes abduction of the eye, is innervated by the abducens nerve. The superior oblique is innervated by the trochlear nerve. All of the other muscles are innervated by the oculomotor nerve, as is the levator palpebrae superioris. The motor nuclei of these cranial nerves connect to the brain stem, which coordinates eye movements.

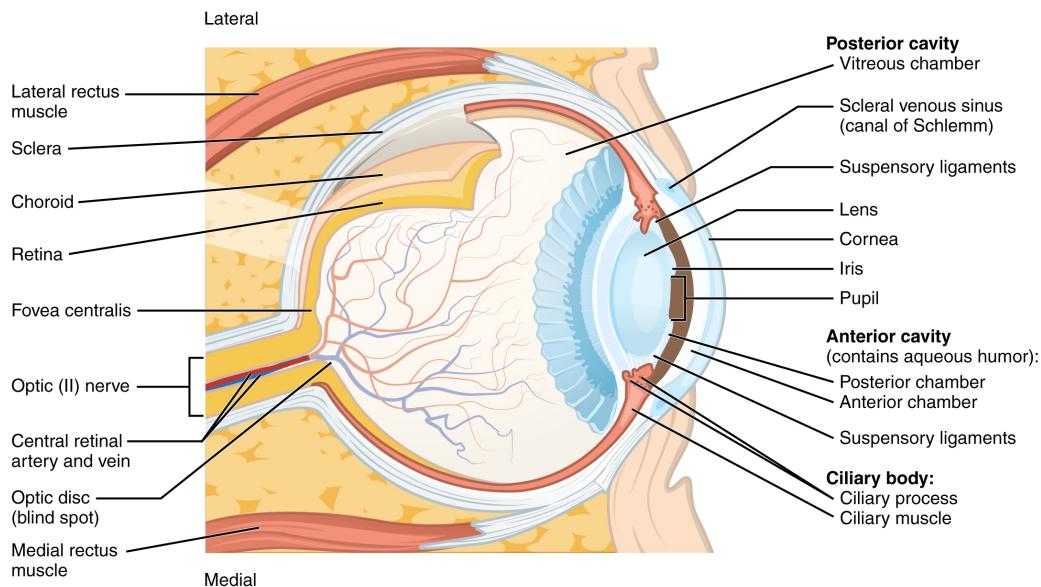


**FIGURE 14.14 Extraocular Muscles** The extraocular muscles move the eye within the orbit.

The eye itself is a hollow sphere composed of three layers of tissue. The outermost layer is the **fibrous tunic**, which includes the white **sclera** and clear **cornea**. The sclera accounts for five sixths of the surface of the eye, most of which is not visible, though humans are unique compared with many other species in having so much of the “white of the eye” visible (Figure 14.15). The transparent cornea covers the anterior tip of the eye and allows light to enter the eye. The middle layer of the eye is the **vascular tunic**, which is mostly composed of the choroid, ciliary body, and iris. The **choroid** is a layer of highly vascularized connective tissue that provides a blood supply to the eyeball. The choroid is posterior to the **ciliary body**, a muscular structure that is attached to the **lens** by suspensory ligaments, or **zonule fibers**. These two structures bend the lens, allowing it to focus light on the back of the eye. Overlaying the ciliary body, and visible in the anterior eye, is the **iris**—the colored part of the eye. The iris is a smooth muscle that opens or closes the **pupil**, which is the hole at the center of the eye that allows light to enter. The iris constricts the pupil in response to bright light and dilates the pupil in response to dim light. The innermost layer of the eye is the **neural tunic**, or **retina**, which contains the nervous tissue responsible for photoreception.

The eye is also divided into two cavities: the anterior cavity and the posterior cavity. The anterior cavity is the space between the cornea and lens, including the iris and ciliary body. It is filled with a watery fluid called the **aqueous humor**. The posterior cavity is the space behind the lens that extends to the posterior side of the interior eyeball, where the retina is located. The posterior cavity is filled with a more viscous fluid called the **vitreous humor**.

The retina is composed of several layers and contains specialized cells for the initial processing of visual stimuli. The photoreceptors (rods and cones) change their membrane potential when stimulated by light energy. The change in membrane potential alters the amount of neurotransmitter that the photoreceptor cells release onto **bipolar cells** in the **outer synaptic layer**. It is the bipolar cell in the retina that connects a photoreceptor to a **retinal ganglion cell (RGC)** in the **inner synaptic layer**. There, **amacrine cells** additionally contribute to retinal processing before an action potential is produced by the RGC. The axons of RGCs, which lie at the innermost layer of the retina, collect at the **optic disc** and leave the eye as the **optic nerve** (see Figure 14.15). Because these axons pass through the retina, there are no photoreceptors at the very back of the eye, where the optic nerve begins. This creates a “blind spot” in the retina, and a corresponding blind spot in our visual field.

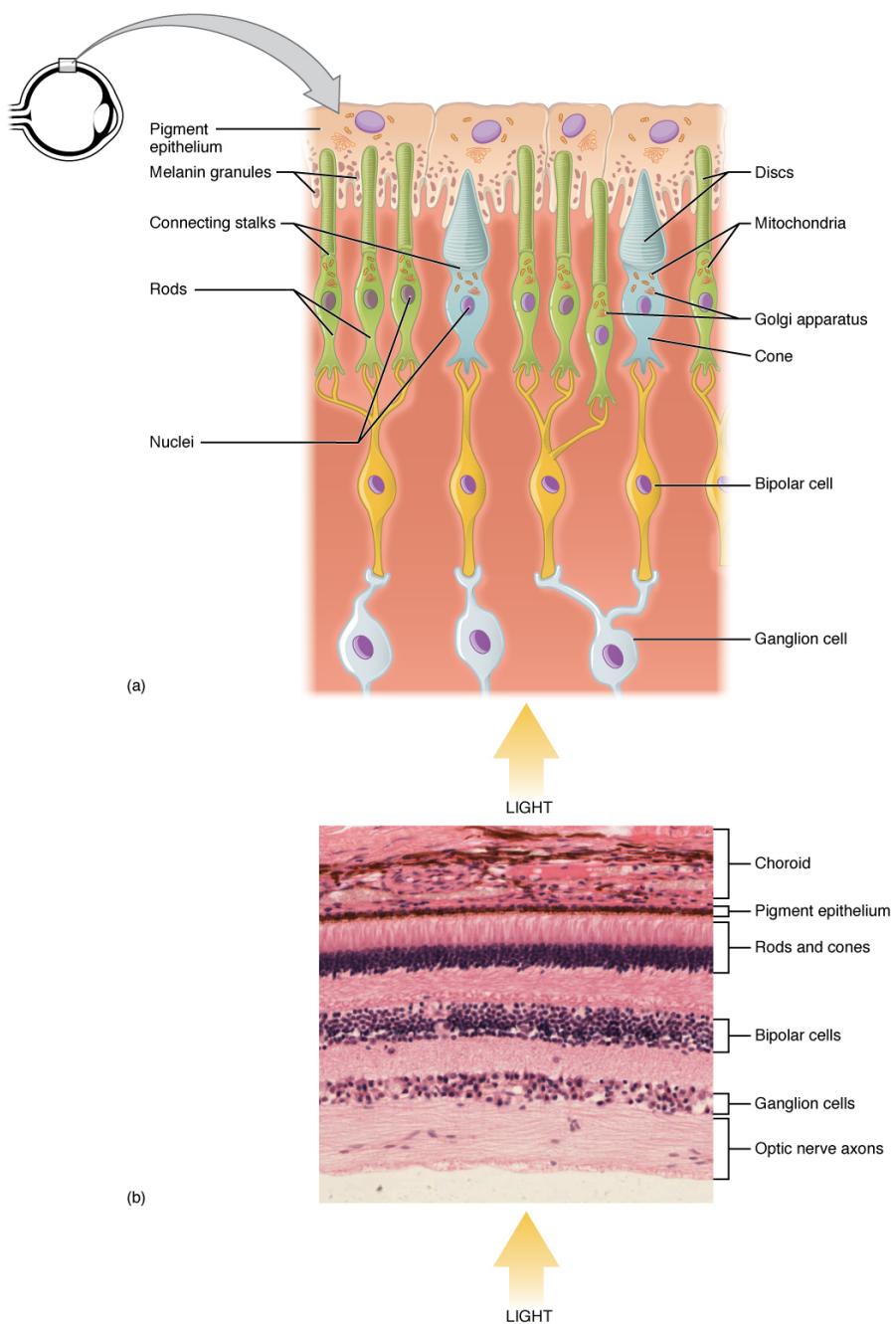


**FIGURE 14.15 Structure of the Eye** The sphere of the eye can be divided into anterior and posterior chambers. The wall of the eye is composed of three layers: the fibrous tunic, vascular tunic, and neural tunic. Within the neural tunic is the retina, with three layers of cells and two synaptic layers in between. The center of the retina has a small indentation known as the fovea.

Note that the photoreceptors in the retina (rods and cones) are located behind the axons, RGCs, bipolar cells, and retinal blood vessels. A significant amount of light is absorbed by these structures before the light reaches the photoreceptor cells. However, at the exact center of the retina is a small area known as the **fovea**. At the fovea, the retina lacks the supporting cells and blood vessels, and only contains photoreceptors. Therefore, **visual acuity**, or the sharpness of vision, is greatest at the fovea. This is because the fovea is where the least amount of incoming light is absorbed by other retinal structures (see Figure 14.15). As one moves in either direction from this central

point of the retina, visual acuity drops significantly. In addition, each photoreceptor cell of the fovea is connected to a single RGC. Therefore, this RGC does not have to integrate inputs from multiple photoreceptors, which reduces the accuracy of visual transduction. Toward the edges of the retina, several photoreceptors converge on RGCs (through the bipolar cells) up to a ratio of 50 to 1. The difference in visual acuity between the fovea and peripheral retina is easily evidenced by looking directly at a word in the middle of this paragraph. The visual stimulus in the middle of the field of view falls on the fovea and is in the sharpest focus. Without moving your eyes off that word, notice that words at the beginning or end of the paragraph are not in focus. The images in your peripheral vision are focused by the peripheral retina, and have vague, blurry edges and words that are not as clearly identified. As a result, a large part of the neural function of the eyes is concerned with moving the eyes and head so that important visual stimuli are centered on the fovea.

Light falling on the retina causes chemical changes to pigment molecules in the photoreceptors, ultimately leading to a change in the activity of the RGCs. Photoreceptor cells have two parts, the **inner segment** and the **outer segment** (Figure 14.16). The inner segment contains the nucleus and other common organelles of a cell, whereas the outer segment is a specialized region in which photoreception takes place. There are two types of photoreceptors—rods and cones—which differ in the shape of their outer segments. The rod-shaped outer segments of the **rod photoreceptor** contain a stack of membrane-bound discs that contain the photosensitive pigment **rhodopsin**. The cone-shaped outer segments of the **cone photoreceptor** contain their photosensitive pigments in infoldings of the cell membrane. There are three cone photopigments, called **opsins**, which are each sensitive to a particular wavelength of light. The wavelength of visible light determines its color. The pigments in human eyes are specialized in perceiving three different primary colors: red, green, and blue.



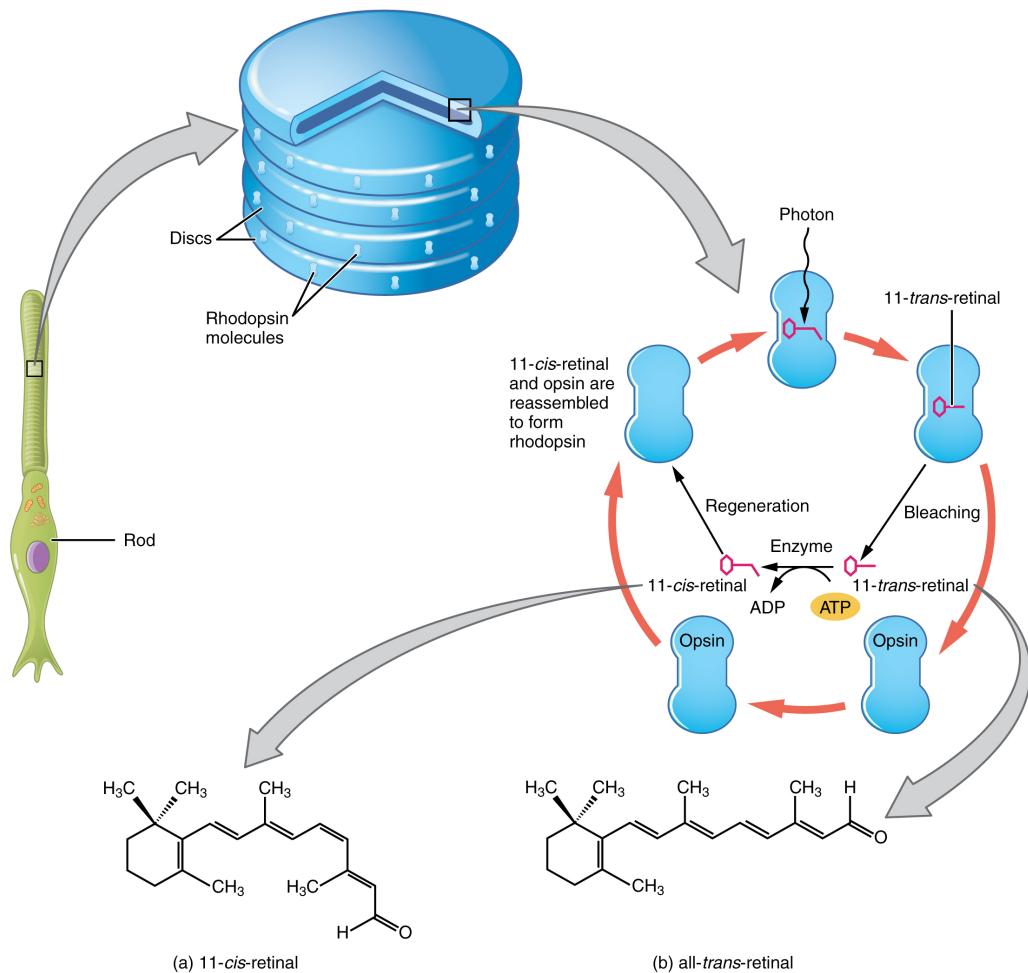
**FIGURE 14.16 Photoreceptor** (a) All photoreceptors have inner segments containing the nucleus and other important organelles and outer segments with membrane arrays containing the photosensitive opsin molecules. Rod outer segments are long columnar shapes with stacks of membrane-bound discs that contain the rhodopsin pigment. Cone outer segments are short, tapered shapes with folds of membrane in place of the discs in the rods. (b) Tissue of the retina shows a dense layer of nuclei of the rods and cones. LM  $\times 800$ . (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

At the molecular level, visual stimuli cause changes in the photopigment molecule that lead to changes in membrane potential of the photoreceptor cell. A single unit of light is called a **photon**, which is described in physics as a packet of energy with properties of both a particle and a wave. The energy of a photon is represented by its wavelength, with each wavelength of visible light corresponding to a particular color. Visible light is electromagnetic radiation with a wavelength between 380 and 720 nm. Wavelengths of electromagnetic radiation longer than 720 nm fall into the infrared range, whereas wavelengths shorter than 380 nm fall into the ultraviolet range. Light with a wavelength of 380 nm is blue whereas light with a wavelength of 720 nm is dark red. All other colors fall between red and blue at various points along the wavelength scale.

Opsin pigments are actually transmembrane proteins that contain a cofactor known as **retinal**. Retinal is a

hydrocarbon molecule related to vitamin A. When a photon hits retinal, the long hydrocarbon chain of the molecule is biochemically altered. Specifically, photons cause some of the double-bonded carbons within the chain to switch from a *cis* to a *trans* conformation. This process is called **photoisomerization**. Before interacting with a photon, retinal's flexible double-bonded carbons are in the *cis* conformation. This molecule is referred to as 11-*cis*-retinal. A photon interacting with the molecule causes the flexible double-bonded carbons to change to the *trans*-conformation, forming all-*trans*-retinal, which has a straight hydrocarbon chain (Figure 14.17).

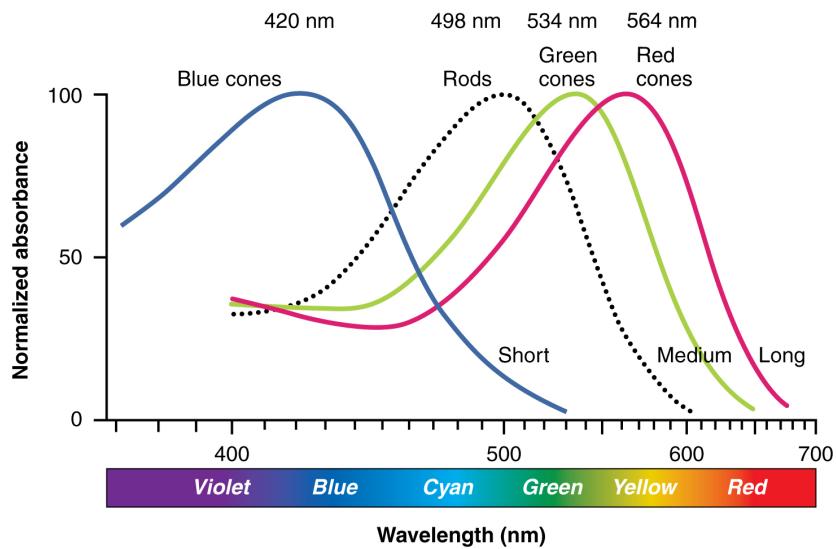
The shape change of retinal in the photoreceptors initiates visual transduction in the retina. Activation of retinal and the opsin proteins result in activation of a G protein. The G protein changes the membrane potential of the photoreceptor cell, which then releases less neurotransmitter into the outer synaptic layer of the retina. Until the retinal molecule is changed back to the 11-*cis*-retinal shape, the opsin cannot respond to light energy, which is called bleaching. When a large group of photopigments is bleached, the retina will send information as if opposing visual information is being perceived. After a bright flash of light, afterimages are usually seen in negative. The photoisomerization is reversed by a series of enzymatic changes so that the retinal responds to more light energy.



**FIGURE 14.17 Retinal Isomers** The retinal molecule has two isomers, (a) one before a photon interacts with it and (b) one that is altered through photoisomerization.

The opsins are sensitive to limited wavelengths of light. Rhodopsin, the photopigment in rods, is most sensitive to light at a wavelength of 498 nm. The three color opsins have peak sensitivities of 564 nm, 534 nm, and 420 nm corresponding roughly to the primary colors of red, green, and blue (Figure 14.18). The absorbance of rhodopsin in the rods is much more sensitive than in the cone opsins; specifically, rods are sensitive to vision in low light conditions, and cones are sensitive to brighter conditions. In normal sunlight, rhodopsin will be constantly bleached while the cones are active. In a darkened room, there is not enough light to activate cone opsins, and vision is entirely dependent on rods. Rods are so sensitive to light that a single photon can result in an action potential from a rod's corresponding RGC.

The three types of cone opsins, being sensitive to different wavelengths of light, provide us with color vision. By comparing the activity of the three different cones, the brain can extract color information from visual stimuli. For example, a bright blue light that has a wavelength of approximately 450 nm would activate the “red” cones minimally, the “green” cones marginally, and the “blue” cones predominantly. The relative activation of the three different cones is calculated by the brain, which perceives the color as blue. However, cones cannot react to low-intensity light, and rods do not sense the color of light. Therefore, our low-light vision is—in essence—in grayscale. In other words, in a dark room, everything appears as a shade of gray. If you think that you can see colors in the dark, it is most likely because your brain knows what color something is and is relying on that memory.



**FIGURE 14.18 Comparison of Color Sensitivity of Photopigments** Comparing the peak sensitivity and absorbance spectra of the four photopigments suggests that they are most sensitive to particular wavelengths.

## INTERACTIVE LINK

Watch this [video \(<http://openstax.org/l/occipital>\)](http://openstax.org/l/occipital) to learn more about a transverse section through the brain that depicts the visual pathway from the eye to the occipital cortex. The first half of the pathway is the projection from the RGCs through the optic nerve to the lateral geniculate nucleus in the thalamus on either side. This first fiber in the pathway synapses on a thalamic cell that then projects to the visual cortex in the occipital lobe where “seeing,” or visual perception, takes place. This video gives an abbreviated overview of the visual system by concentrating on the pathway from the eyes to the occipital lobe. The video makes the statement (at 0:45) that “specialized cells in the retina called ganglion cells convert the light rays into electrical signals.” What aspect of retinal processing is simplified by that statement? Explain your answer.

## Sensory Nerves

Once any sensory cell transduces a stimulus into a nerve impulse, that impulse has to travel along axons to reach the CNS. In many of the special senses, the axons leaving the sensory receptors have a **topographical** arrangement, meaning that the location of the sensory receptor relates to the location of the axon in the nerve. For example, in the retina, axons from RGCs in the fovea are located at the center of the optic nerve, where they are surrounded by axons from the more peripheral RGCs.

## Spinal Nerves

Generally, spinal nerves contain afferent axons from sensory receptors in the periphery, such as from the skin, mixed with efferent axons travelling to the muscles or other effector organs. As the spinal nerve nears the spinal cord, it splits into dorsal and ventral roots. The dorsal root contains only the axons of sensory neurons, whereas the ventral roots contain only the axons of the motor neurons. Some of the branches will synapse with local neurons in the dorsal root ganglion, posterior (dorsal) horn, or even the anterior (ventral) horn, at the level of the spinal cord where they enter. Other branches will travel a short distance up or down the spine to interact with neurons at other levels of the spinal cord. A branch may also turn into the posterior (dorsal) column of the white matter to connect

with the brain. For the sake of convenience, we will use the terms ventral and dorsal in reference to structures within the spinal cord that are part of these pathways. This will help to underscore the relationships between the different components. Typically, spinal nerve systems that connect to the brain are **contralateral**, in that the right side of the body is connected to the left side of the brain and the left side of the body to the right side of the brain.

### Cranial Nerves

Cranial nerves convey specific sensory information from the head and neck directly to the brain. Whereas spinal information is contralateral, cranial nerve systems, with some exceptions, are mostly **ipsilateral**, meaning that a cranial nerve on the right side of the head is connected to the right side of the brain. Some cranial nerves contain only sensory axons, such as the olfactory, optic, and vestibulocochlear nerves. Other cranial nerves contain both sensory and motor axons, including the trigeminal, facial, glossopharyngeal, and vagus nerves (however, the vagus nerve is not associated with the somatic nervous system). The general senses of somatosensation for the face travel through the trigeminal system.

## 14.2 Central Processing

### LEARNING OBJECTIVES

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

- Describe the pathways that sensory systems follow into the central nervous system
- Differentiate between the two major ascending pathways in the spinal cord
- Describe the pathway of somatosensory input from the face and compare it to the ascending pathways in the spinal cord
- Explain topographical representations of sensory information in at least two systems
- Describe two pathways of visual processing and the functions associated with each

### Sensory Pathways

Specific regions of the CNS coordinate different somatic processes using sensory inputs and motor outputs of peripheral nerves. A simple case is a reflex caused by a synapse between a dorsal sensory neuron axon and a motor neuron in the ventral horn. More complex arrangements are possible to integrate peripheral sensory information with higher processes. The important regions of the CNS that play a role in somatic processes can be separated into the spinal cord, brain stem, diencephalon, cerebral cortex, and subcortical structures.

#### Spinal Cord and Brain Stem

A sensory pathway that carries peripheral sensations to the brain is referred to as an **ascending pathway**, or ascending tract. The various sensory modalities each follow specific pathways through the CNS. Tactile and other somatosensory stimuli activate receptors in the skin, muscles, tendons, and joints throughout the entire body. However, the somatosensory pathways are divided into two separate systems on the basis of the location of the receptor neurons. Somatosensory stimuli from below the neck pass along the sensory pathways of the spinal cord, whereas somatosensory stimuli from the head and neck travel through the cranial nerves—specifically, the trigeminal system.

The **dorsal column system** (sometimes referred to as the dorsal column–medial lemniscus) and the **spinothalamic tract** are two major pathways that bring sensory information to the brain ([Figure 14.19](#)). The sensory pathways in each of these systems are composed of three successive neurons.

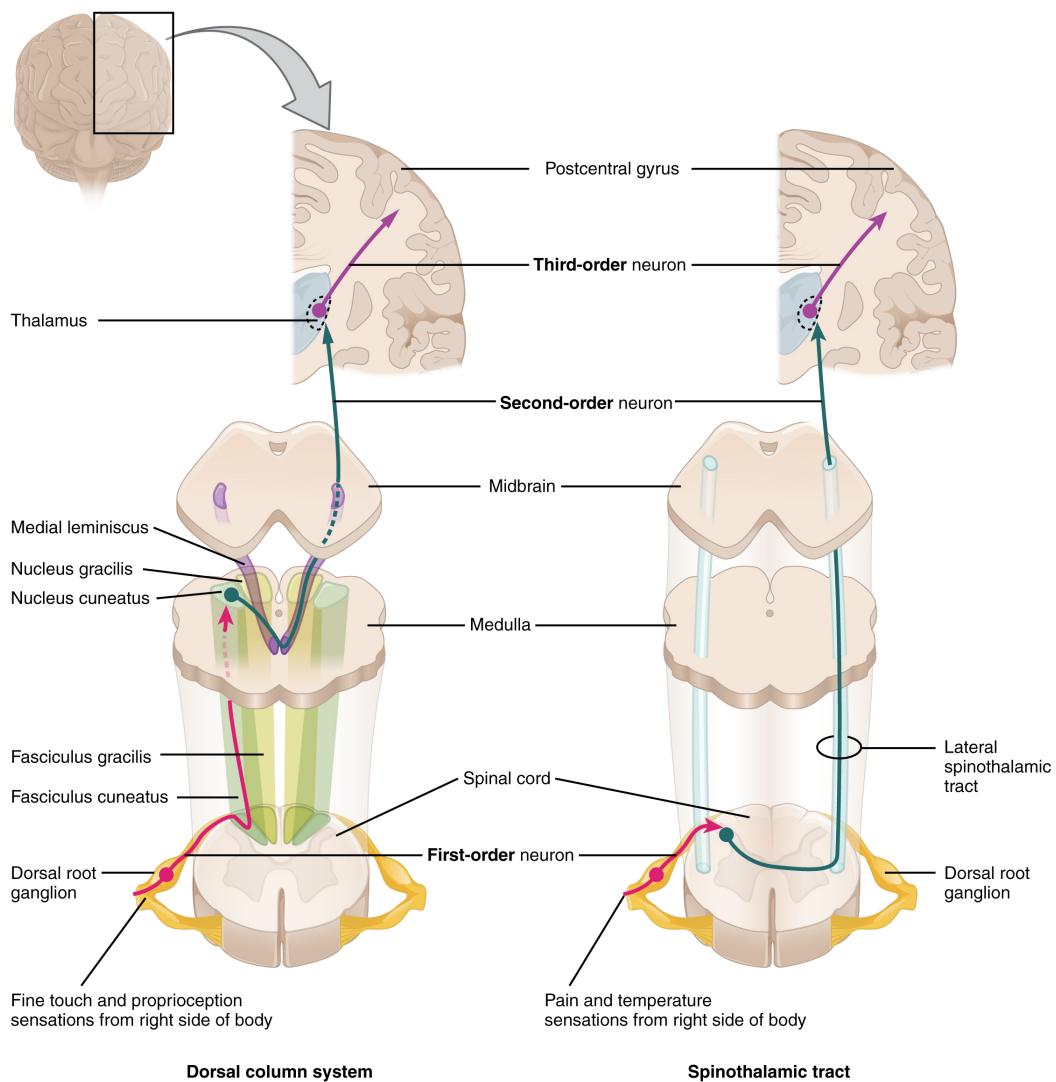
The dorsal column system begins with the axon of a dorsal root ganglion neuron entering the dorsal root and joining the dorsal column white matter in the spinal cord. As axons of this pathway enter the dorsal column, they take on a positional arrangement so that axons from lower levels of the body position themselves medially, whereas axons from upper levels of the body position themselves laterally. The dorsal column is separated into two component tracts, the **fasciculus gracilis** that contains axons from the legs and lower body, and the **fasciculus cuneatus** that contains axons from the upper body and arms.

The axons in the dorsal column terminate in the nuclei of the medulla, where each synapses with the second neuron in their respective pathway. The **nucleus gracilis** is the target of fibers in the fasciculus gracilis, whereas the **nucleus cuneatus** is the target of fibers in the fasciculus cuneatus. The second neuron in the system projects from one of the two nuclei and then **decussates**, or crosses the midline of the medulla. These axons then continue to

ascend the brain stem as a bundle called the **medial lemniscus**. These axons terminate in the thalamus, where each synapses with the third neuron in their respective pathway. The third neuron in the system projects its axons to the postcentral gyrus of the cerebral cortex, where somatosensory stimuli are initially processed and the conscious perception of the stimulus occurs.

The spinothalamic tract also begins with neurons in a dorsal root ganglion. These neurons extend their axons to the dorsal horn, where they synapse with the second neuron in their respective pathway. The name “spinothalamic” comes from this second neuron, which has its cell body in the spinal cord gray matter and connects to the thalamus. Axons from these second neurons then decussate within the spinal cord and ascend to the brain and enter the thalamus, where each synapses with the third neuron in its respective pathway. The neurons in the thalamus then project their axons to the spinothalamic tract, which synapses in the postcentral gyrus of the cerebral cortex.

These two systems are similar in that they both begin with dorsal root ganglion cells, as with most general sensory information. The dorsal column system is primarily responsible for touch sensations and proprioception, whereas the spinothalamic tract pathway is primarily responsible for pain and temperature sensations. Another similarity is that the second neurons in both of these pathways are contralateral, because they project across the midline to the other side of the brain or spinal cord. In the dorsal column system, this decussation takes place in the brain stem; in the spinothalamic pathway, it takes place in the spinal cord at the same spinal cord level at which the information entered. The third neurons in the two pathways are essentially the same. In both, the second neuron synapses in the thalamus, and the thalamic neuron projects to the somatosensory cortex.



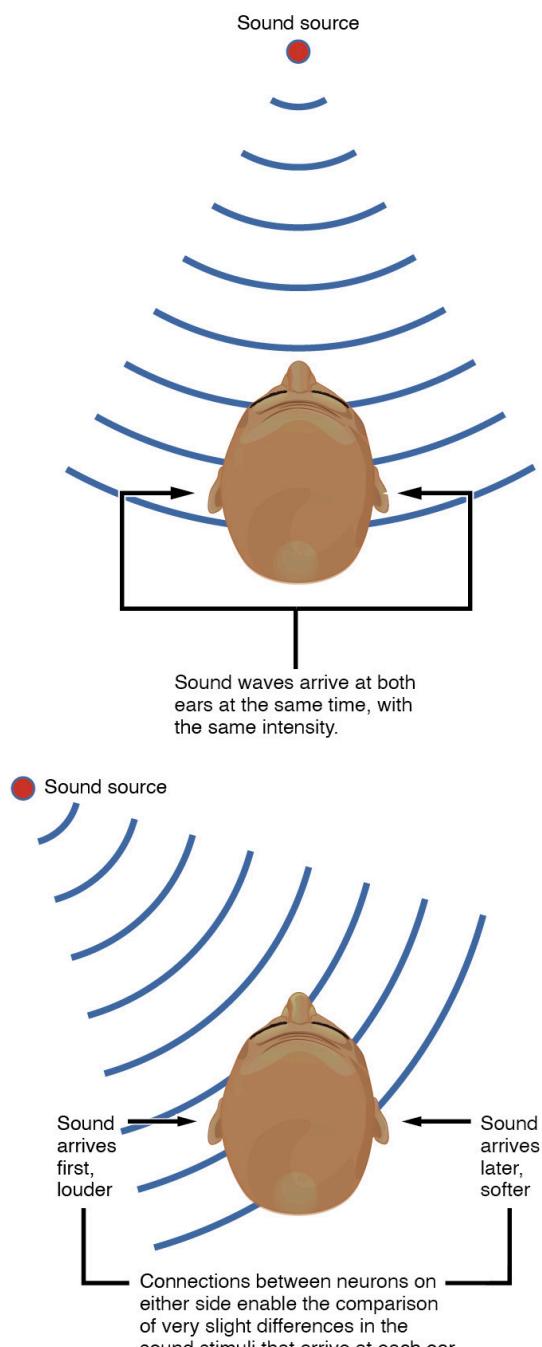
**FIGURE 14.19 Anterior View of Ascending Sensory Pathways of the Spinal Cord** The dorsal column system and spinothalamic tract are the major ascending pathways that connect the periphery with the brain.

The trigeminal pathway carries somatosensory information from the face, head, mouth, and nasal cavity. As with the previously discussed nerve tracts, the sensory pathways of the trigeminal pathway each involve three successive neurons. First, axons from the trigeminal ganglion enter the brain stem at the level of the pons. These axons project to one of three locations. The **spinal trigeminal nucleus** of the medulla receives information similar to that carried by spinothalamic tract, such as pain and temperature sensations. Other axons go to either the **chief sensory nucleus** in the pons or the **mesencephalic nuclei** in the midbrain. These nuclei receive information like that carried by the dorsal column system, such as touch, pressure, vibration, and proprioception. Axons from the second neuron decussate and ascend to the thalamus along the trigeminothalamic tract. In the thalamus, each axon synapses with the third neuron in its respective pathway. Axons from the third neuron then project from the thalamus to the primary somatosensory cortex of the cerebrum.

The sensory pathway for gustation travels along the facial and glossopharyngeal cranial nerves, which synapse with neurons of the **solitary nucleus** in the brain stem. Axons from the solitary nucleus then project to the **ventral posterior nucleus** of the thalamus. Finally, axons from the ventral posterior nucleus project to the gustatory cortex of the cerebral cortex, where taste is processed and consciously perceived.

The sensory pathway for audition travels along the vestibulocochlear nerve, which synapses with neurons in the cochlear nuclei of the superior medulla. Within the brain stem, input from either ear is combined to extract location information from the auditory stimuli. Whereas the initial auditory stimuli received at the cochlea strictly represent the frequency—or pitch—of the stimuli, the locations of sounds can be determined by comparing information arriving at both ears.

Sound localization is a feature of central processing in the auditory nuclei of the brain stem. Sound localization is achieved by the brain calculating the **interaural time difference** and the **interaural intensity difference**. A sound originating from a specific location will arrive at each ear at different times, unless the sound is directly in front of the listener. If the sound source is slightly to the left of the listener, the sound will arrive at the left ear microseconds before it arrives at the right ear ([Figure 14.20](#)). This time difference is an example of an interaural time difference. Also, the sound will be slightly louder in the left ear than in the right ear because some of the sound waves reaching the opposite ear are blocked by the head. This is an example of an interaural intensity difference.



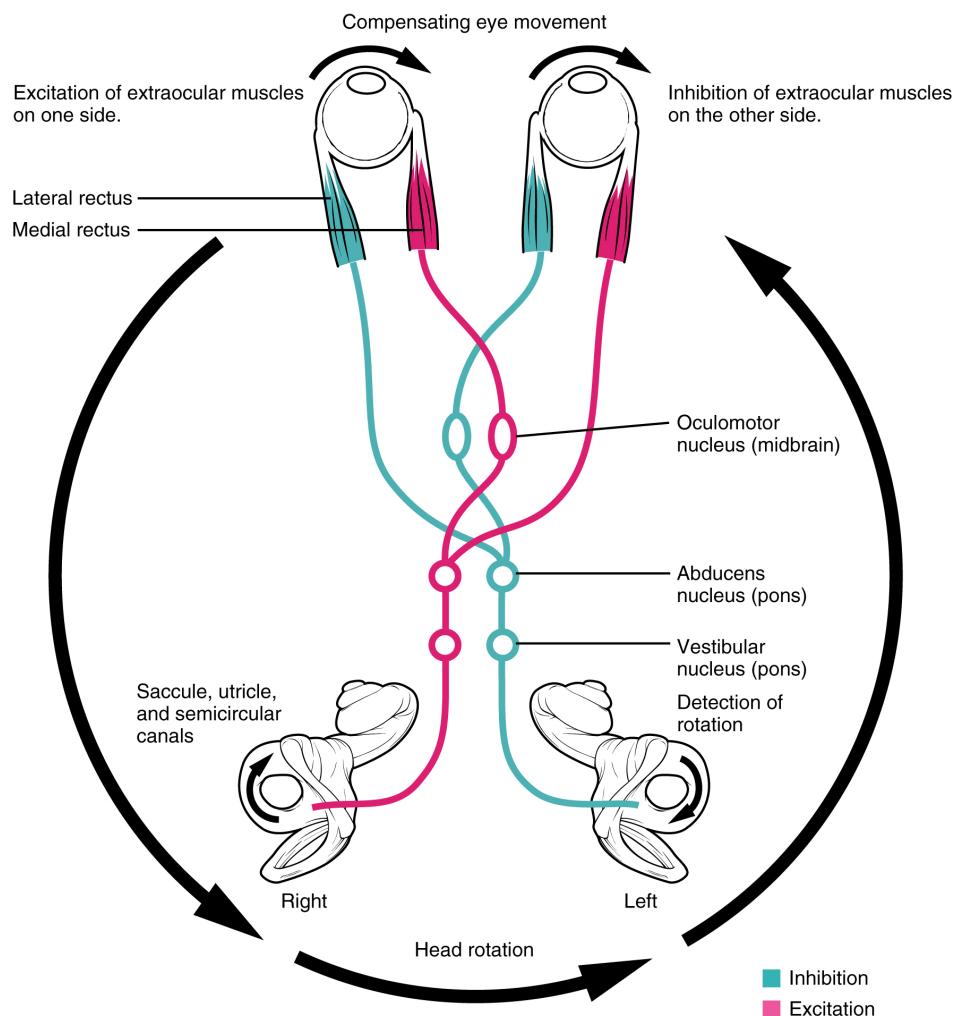
**FIGURE 14.20 Auditory Brain Stem Mechanisms of Sound Localization** Localizing sound in the horizontal plane is achieved by processing in the medullary nuclei of the auditory system. Connections between neurons on either side are able to compare very slight differences in sound stimuli that arrive at either ear and represent interaural time and intensity differences.

Auditory processing continues on to a nucleus in the midbrain called the **inferior colliculus**. Axons from the inferior colliculus project to two locations, the thalamus and the **superior colliculus**. The **medial geniculate nucleus** of the thalamus receives the auditory information and then projects that information to the auditory cortex in the temporal lobe of the cerebral cortex. The superior colliculus receives input from the visual and somatosensory systems, as well as the ears, to initiate stimulation of the muscles that turn the head and neck toward the auditory stimulus.

Balance is coordinated through the vestibular system, the nerves of which are composed of axons from the vestibular ganglion that carries information from the utricle, saccule, and semicircular canals. The system contributes to controlling head and neck movements in response to vestibular signals. An important function of the vestibular system is coordinating eye and head movements to maintain visual attention. Most of the axons terminate in the **vestibular nuclei** of the medulla. Some axons project from the vestibular ganglion directly to the cerebellum,

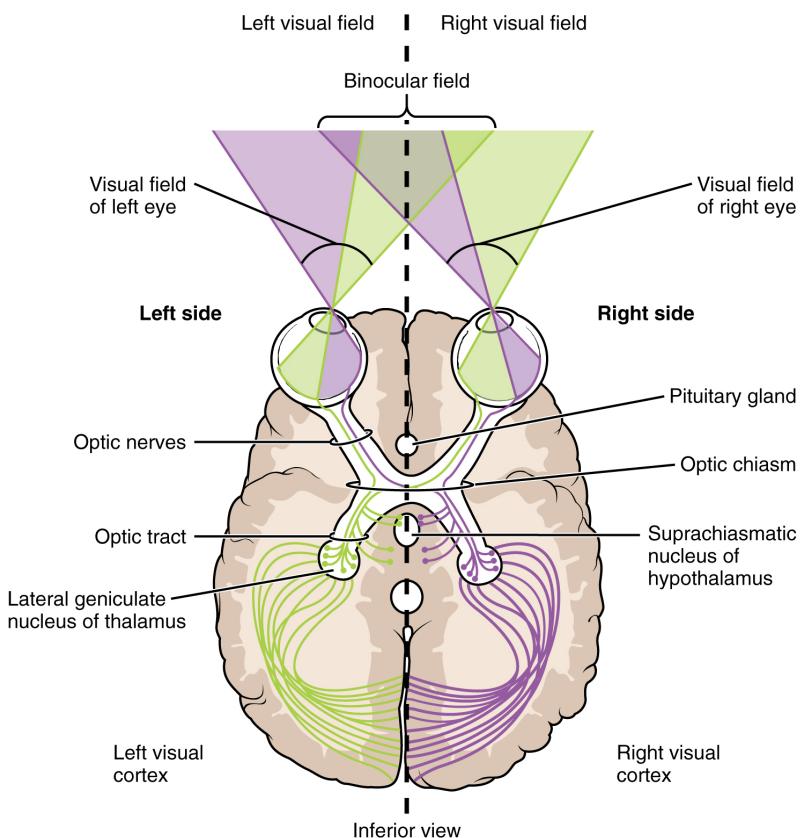
with no intervening synapse in the vestibular nuclei. The cerebellum is primarily responsible for initiating movements on the basis of equilibrium information.

Neurons in the vestibular nuclei project their axons to targets in the brain stem, which influences respiratory and cardiovascular functions in relation to body movements. A second target of the axons of neurons in the vestibular nuclei is the spinal cord, which initiates the spinal reflexes involved with posture and balance. To assist the visual system, fibers of the vestibular nuclei project to the oculomotor, trochlear, and abducens nuclei to influence signals sent along the cranial nerves. These connections constitute the pathway of the **vestibulo-ocular reflex (VOR)**, which compensates for head and body movement by stabilizing images on the retina (Figure 14.21). Finally, the vestibular nuclei project to the thalamus to join the proprioceptive pathway of the dorsal column system, allowing conscious perception of equilibrium.



**FIGURE 14.21** **Vestibulo-ocular Reflex** Connections between the vestibular system and the cranial nerves controlling eye movement keep the eyes centered on a visual stimulus, even though the head is moving. During head movement, the eye muscles move the eyes in the opposite direction as the head movement, keeping the visual stimulus centered in the field of view.

The connections of the optic nerve are more complicated than those of other cranial nerves. Instead of the connections being between each eye and the brain, visual information is segregated between the left and right sides of the visual field. In addition, some of the information from one side of the visual field projects to the opposite side of the brain. Within each eye, the axons projecting from the medial side of the retina decussate at the **optic chiasm**. For example, the axons from the medial retina of the left eye cross over to the right side of the brain at the optic chiasm. However, within each eye, the axons projecting from the lateral side of the retina do not decussate. For example, the axons from the lateral retina of the right eye project back to the right side of the brain. Therefore the left field of view of each eye is processed on the right side of the brain, whereas the right field of view of each eye is processed on the left side of the brain (Figure 14.22).



**FIGURE 14.22 Segregation of Visual Field Information at the Optic Chiasm** Contralateral visual field information from the lateral retina projects to the ipsilateral brain, whereas ipsilateral visual field information has to decussate at the optic chiasm to reach the opposite side of the brain. (Note that this is an inferior view.)

A unique clinical presentation that relates to this anatomic arrangement is the loss of lateral peripheral vision, known as bilateral hemianopia. This is different from “tunnel vision” because the superior and inferior peripheral fields are not lost. Visual field deficits can be disturbing for a patient, but in this case, the cause is not within the visual system itself. A growth of the pituitary gland presses against the optic chiasm and interferes with signal transmission. However, the axons projecting to the same side of the brain are unaffected. Therefore, the patient loses the outermost areas of their field of vision and cannot see objects to their right and left.

Extending from the optic chiasm, the axons of the visual system are referred to as the **optic tract** instead of the optic nerve. The optic tract has three major targets, two in the diencephalon and one in the midbrain. The connection between the eyes and diencephalon is demonstrated during development, in which the neural tissue of the retina differentiates from that of the diencephalon by the growth of the secondary vesicles. The connections of the retina into the CNS are a holdover from this developmental association. The majority of the connections of the optic tract are to the thalamus—specifically, the **lateral geniculate nucleus**. Axons from this nucleus then project to the visual cortex of the cerebrum, located in the occipital lobe. Another target of the optic tract is the superior colliculus.

In addition, a very small number of RGC axons project from the optic chiasm to the **suprachiasmatic nucleus** of the hypothalamus. These RGCs are photosensitive, in that they respond to the presence or absence of light. Unlike the photoreceptors, however, these photosensitive RGCs cannot be used to perceive images. By simply responding to the absence or presence of light, these RGCs can send information about day length. The perceived proportion of sunlight to darkness establishes the **circadian rhythm** of our bodies, allowing certain physiological events to occur at approximately the same time every day.

### Diencephalon

The diencephalon is beneath the cerebrum and includes the thalamus and hypothalamus. In the somatic nervous system, the thalamus is an important relay for communication between the cerebrum and the rest of the nervous system. The hypothalamus has both somatic and autonomic functions. In addition, the hypothalamus communicates with the limbic system, which controls emotions and memory functions.

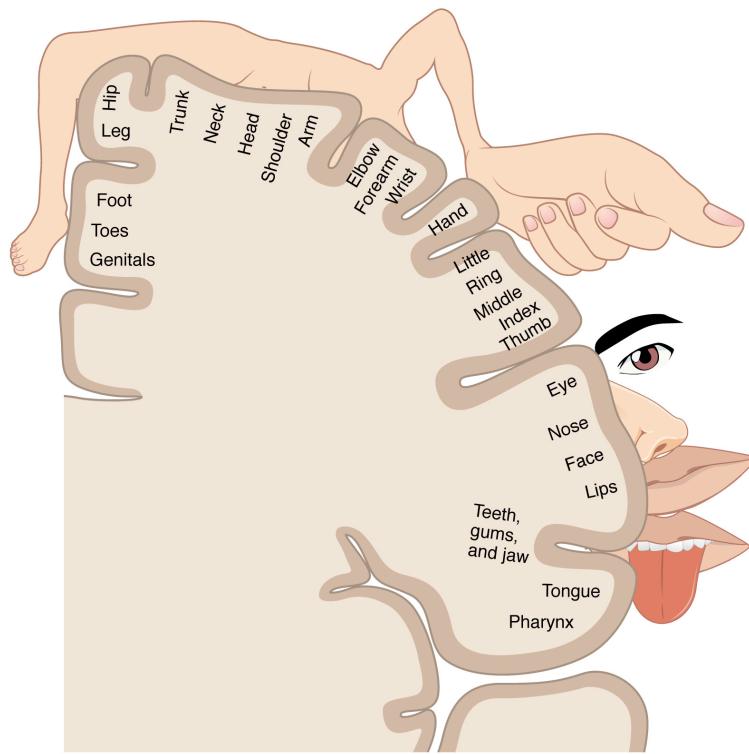
Sensory input to the thalamus comes from most of the special senses and ascending somatosensory tracts. Each sensory system is relayed through a particular nucleus in the thalamus. The thalamus is a required transfer point for most sensory tracts that reach the cerebral cortex, where conscious sensory perception begins. The one exception to this rule is the olfactory system. The olfactory tract axons from the olfactory bulb project directly to the cerebral cortex, along with the limbic system and hypothalamus.

The thalamus is a collection of several nuclei that can be categorized into three anatomical groups. White matter running through the thalamus defines the three major regions of the thalamus, which are an anterior nucleus, a medial nucleus, and a lateral group of nuclei. The anterior nucleus serves as a relay between the hypothalamus and the emotion and memory-producing limbic system. The medial nuclei serve as a relay for information from the limbic system and basal ganglia to the cerebral cortex. This allows memory creation during learning, but also determines alertness. The special and somatic senses connect to the lateral nuclei, where their information is relayed to the appropriate sensory cortex of the cerebrum.

## Cortical Processing

As described earlier, many of the sensory axons are positioned in the same way as their corresponding receptor cells in the body. This allows identification of the position of a stimulus on the basis of which receptor cells are sending information. The cerebral cortex also maintains this sensory topography in the particular areas of the cortex that correspond to the position of the receptor cells. The somatosensory cortex provides an example in which, in essence, the locations of the somatosensory receptors in the body are mapped onto the somatosensory cortex. This mapping is often depicted using a **sensory homunculus** ([Figure 14.23](#)).

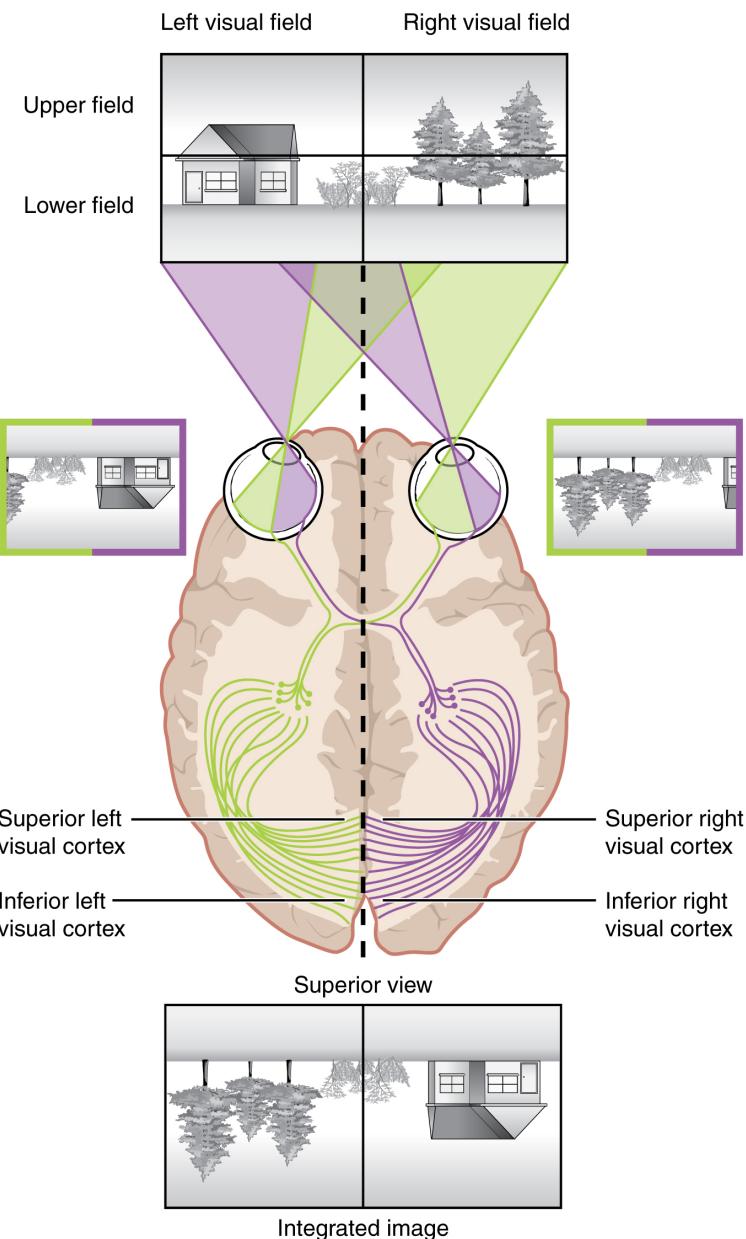
The term homunculus comes from the Latin word for “little man” and refers to a map of the human body that is laid across a portion of the cerebral cortex. In the somatosensory cortex, the external genitals, feet, and lower legs are represented on the medial face of the gyrus within the longitudinal fissure. As the gyrus curves out of the fissure and along the surface of the parietal lobe, the body map continues through the thighs, hips, trunk, shoulders, arms, and hands. The head and face are just lateral to the fingers as the gyrus approaches the lateral sulcus. The representation of the body in this topographical map is medial to lateral from the lower to upper body. It is a continuation of the topographical arrangement seen in the dorsal column system, where axons from the lower body are carried in the fasciculus gracilis, whereas axons from the upper body are carried in the fasciculus cuneatus. As the dorsal column system continues into the medial lemniscus, these relationships are maintained. Also, the head and neck axons running from the trigeminal nuclei to the thalamus run adjacent to the upper body fibers. The connections through the thalamus maintain topography such that the anatomic information is preserved. Note that this correspondence does not result in a perfectly miniature scale version of the body, but rather exaggerates the more sensitive areas of the body, such as the fingers and lower face. Less sensitive areas of the body, such as the shoulders and back, are mapped to smaller areas on the cortex.



**FIGURE 14.23 The Sensory Homunculus** A cartoon representation of the sensory homunculus arranged adjacent to the cortical region in which the processing takes place.

Likewise, the topographic relationship between the retina and the visual cortex is maintained throughout the visual pathway. The visual field is projected onto the two retinæ, as described above, with sorting at the optic chiasm. The right peripheral visual field falls on the medial portion of the right retina and the lateral portion of the left retina. The right medial retina then projects across the midline through the optic chiasm. This results in the right visual field being processed in the left visual cortex. Likewise, the left visual field is processed in the right visual cortex (see [Figure 14.22](#)). Though the chiasm is helping to sort right and left visual information, superior and inferior visual information is maintained topographically in the visual pathway. Light from the superior visual field falls on the inferior retina, and light from the inferior visual field falls on the superior retina. This topography is maintained such that the superior region of the visual cortex processes the inferior visual field and vice versa. Therefore, the visual field information is inverted and reversed as it enters the visual cortex—up is down, and left is right. However, the cortex processes the visual information such that the final conscious perception of the visual field is correct. The topographic relationship is evident in that information from the foveal region of the retina is processed in the center of the primary visual cortex. Information from the peripheral regions of the retina are correspondingly processed toward the edges of the visual cortex. Similar to the exaggerations in the sensory homunculus of the somatosensory cortex, the foveal-processing area of the visual cortex is disproportionately larger than the areas processing peripheral vision.

In an experiment performed in the 1960s, subjects wore prism glasses so that the visual field was inverted before reaching the eye. On the first day of the experiment, subjects would duck when walking up to a table, thinking it was suspended from the ceiling. However, after a few days of acclimation, the subjects behaved as if everything were represented correctly. Therefore, the visual cortex is somewhat flexible in adapting to the information it receives from our eyes ([Figure 14.24](#)).



**FIGURE 14.24 Topographic Mapping of the Retina onto the Visual Cortex** The visual field projects onto the retina through the lenses and falls on the retinae as an inverted, reversed image. The topography of this image is maintained as the visual information travels through the visual pathway to the cortex.

The cortex has been described as having specific regions that are responsible for processing specific information; there is the visual cortex, somatosensory cortex, gustatory cortex, etc. However, our experience of these senses is not divided. Instead, we experience what can be referred to as a seamless percept. Our perceptions of the various sensory modalities—though distinct in their content—are integrated by the brain so that we experience the world as a continuous whole.

In the cerebral cortex, sensory processing begins at the **primary sensory cortex**, then proceeds to an **association area**, and finally, into a **multimodal integration area**. For example, the visual pathway projects from the retinae through the thalamus to the primary visual cortex in the occipital lobe. This area is primarily in the medial wall within the longitudinal fissure. Here, visual stimuli begin to be recognized as basic shapes. Edges of objects are recognized and built into more complex shapes. Also, inputs from both eyes are compared to extract depth information.

Because of the overlapping field of view between the two eyes, the brain can begin to estimate the distance of stimuli based on **binocular depth cues**.

## INTERACTIVE LINK

Watch this [video](http://openstax.org/l/L_3-D1) ([http://openstax.org/l/L\\_3-D1](http://openstax.org/l/L_3-D1)) to learn more about how the brain perceives 3-D motion. Similar to how retinal disparity offers 3-D moviegoers a way to extract 3-D information from the two-dimensional visual field projected onto the retina, the brain can extract information about movement in space by comparing what the two eyes see. If movement of a visual stimulus is leftward in one eye and rightward in the opposite eye, the brain interprets this as movement toward (or away) from the face along the midline. If both eyes see an object moving in the same direction, but at different rates, what would that mean for spatial movement?

### Everyday Connection

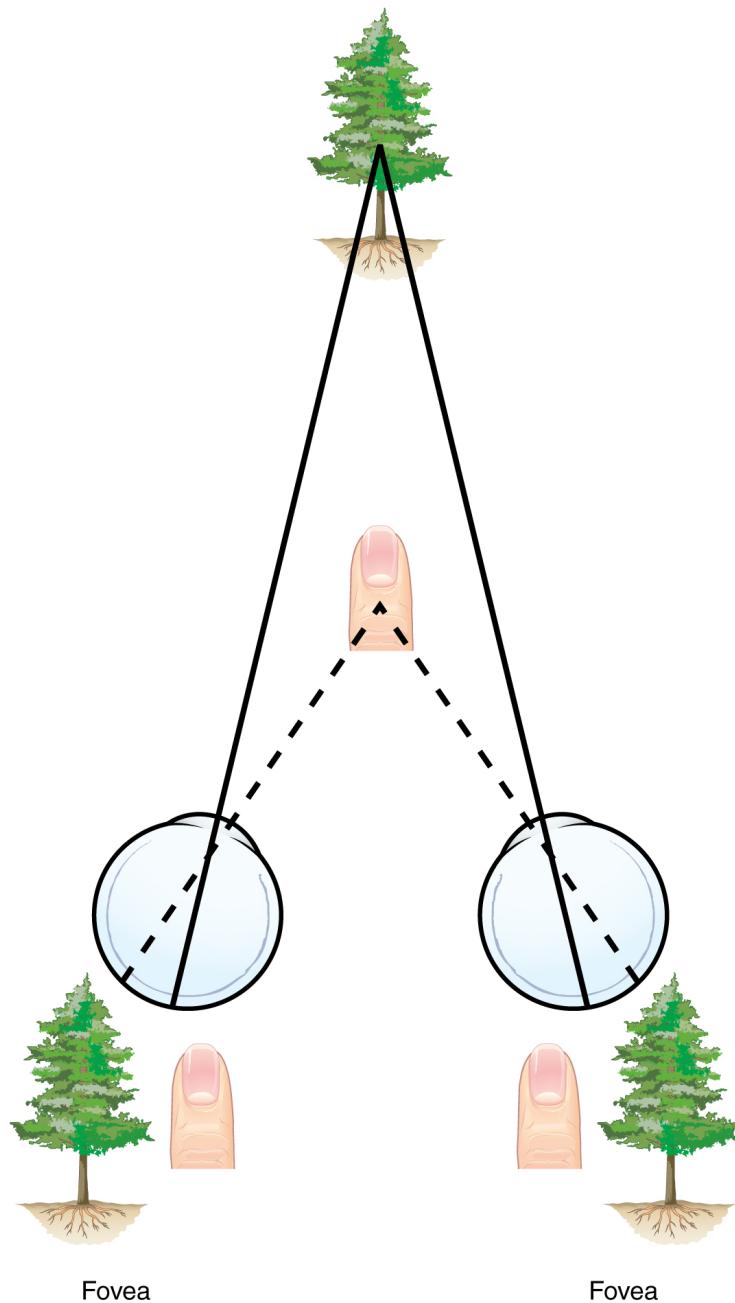
#### Depth Perception, 3-D Movies, and Optical Illusions

The visual field is projected onto the retinal surface, where photoreceptors transduce light energy into neural signals for the brain to interpret. The retina is a two-dimensional surface, so it does not encode three-dimensional information. However, we can perceive depth. How is that accomplished?

Two ways in which we can extract depth information from the two-dimensional retinal signal are based on monocular cues and binocular cues, respectively. Monocular depth cues are those that are the result of information within the two-dimensional visual field. One object that overlaps another object has to be in front. Relative size differences are also a cue. For example, if a basketball appears larger than the basket, then the basket must be further away. On the basis of experience, we can estimate how far away the basket is. Binocular depth cues compare information represented in the two retinae because they do not see the visual field exactly the same.

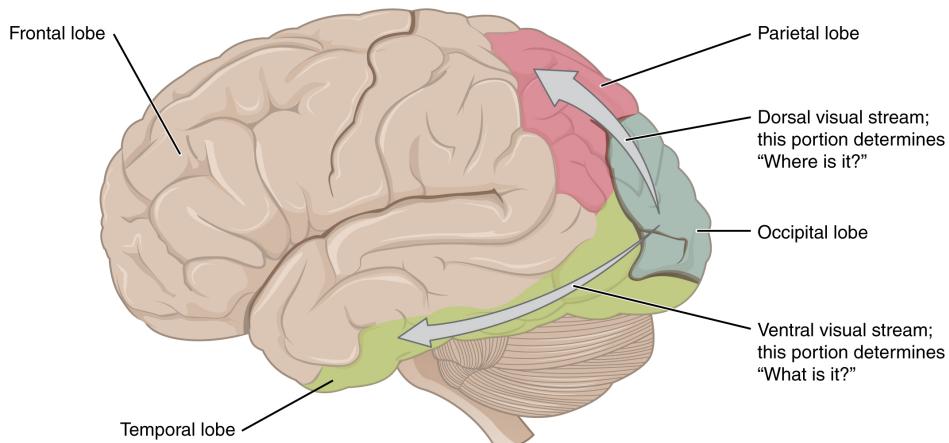
The centers of the two eyes are separated by a small distance, which is approximately 6 to 6.5 cm in most people. Because of this offset, visual stimuli do not fall on exactly the same spot on both retinae unless we are fixated directly on them and they fall on the fovea of each retina. All other objects in the visual field, either closer or farther away than the fixated object, will fall on different spots on the retina. When vision is fixed on an object in space, closer objects will fall on the lateral retina of each eye, and more distant objects will fall on the medial retina of either eye (Figure 14.25). This is easily observed by holding a finger up in front of your face as you look at a more distant object. You will see two images of your finger that represent the two disparate images that are falling on either retina.

These depth cues, both monocular and binocular, can be exploited to make the brain think there are three dimensions in two-dimensional information. This is the basis of 3-D movies. The projected image on the screen is two dimensional, but it has disparate information embedded in it. The 3-D glasses that are available at the theater filter the information so that only one eye sees one version of what is on the screen, and the other eye sees the other version. If you take the glasses off, the image on the screen will have varying amounts of blur because both eyes are seeing both layers of information, and the third dimension will not be evident. Some optical illusions can take advantage of depth cues as well, though those are more often using monocular cues to fool the brain into seeing different parts of the scene as being at different depths.



**FIGURE 14.25 Retinal Disparity** Because of the interocular distance, which results in objects of different distances falling on different spots of the two retinæ, the brain can extract depth perception from the two-dimensional information of the visual field.

There are two main regions that surround the primary cortex that are usually referred to as areas V2 and V3 (the primary visual cortex is area V1). These surrounding areas are the visual association cortex. The visual association regions develop more complex visual perceptions by adding color and motion information. The information processed in these areas is then sent to regions of the temporal and parietal lobes. Visual processing has two separate streams of processing: one into the temporal lobe and one into the parietal lobe. These are the ventral and dorsal streams, respectively (Figure 14.26). The **ventral stream** identifies visual stimuli and their significance. Because the ventral stream uses temporal lobe structures, it begins to interact with the non-visual cortex and may be important in visual stimuli becoming part of memories. The **dorsal stream** locates objects in space and helps in guiding movements of the body in response to visual inputs. The dorsal stream enters the parietal lobe, where it interacts with somatosensory cortical areas that are important for our perception of the body and its movements. The dorsal stream can then influence frontal lobe activity where motor functions originate.



**FIGURE 14.26 Ventral and Dorsal Visual Streams** From the primary visual cortex in the occipital lobe, visual processing continues in two streams—one into the temporal lobe and one into the parietal lobe.

### Disorders of the...

#### Brain: Prosopagnosia

The failures of sensory perception can be unusual and debilitating. A particular sensory deficit that inhibits an important social function of humans is prosopagnosia, or face blindness. The word comes from the Greek words *prosopa*, that means “faces,” and *agnosia*, that means “not knowing.” Some people may feel that they cannot recognize people easily by their faces. However, a person with prosopagnosia cannot recognize the most recognizable people in their respective cultures. They would not recognize the face of a celebrity, an important historical figure, or even a family member like their mother. They may not even recognize their own face.

Prosopagnosia can be caused by trauma to the brain, or it can be present from birth. The exact cause of prosopagnosia and the reason that it happens to some people is unclear. A study of the brains of people born with the deficit found that a specific region of the brain, the anterior fusiform gyrus of the temporal lobe, is often underdeveloped. This region of the brain is concerned with the recognition of visual stimuli and its possible association with memories. Though the evidence is not yet definitive, this region is likely to be where facial recognition occurs.

Though this can be a devastating condition, people who suffer from it can get by—often by using other cues to recognize the people they see. Often, the sound of a person’s voice, or the presence of unique cues such as distinct facial features (a mole, for example) or hair color can help the sufferer recognize a familiar person. In the video on prosopagnosia provided in this section, a woman is shown having trouble recognizing celebrities, family members, and herself. In some situations, she can use other cues to help her recognize faces.

#### INTERACTIVE LINK

The inability to recognize people by their faces is a troublesome problem. It can be caused by trauma, or it may be inborn. Watch this [video \(<http://openstax.org/l/faces>\)](http://openstax.org/l/faces) to learn more about a person who lost the ability to recognize faces as the result of an injury. She cannot recognize the faces of close family members or herself. What other information can a person suffering from prosopagnosia use to figure out whom they are seeing?

## 14.3 Motor Responses

### LEARNING OBJECTIVES

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

- List the components of the basic processing stream for the motor system
- Describe the pathway of descending motor commands from the cortex to the skeletal muscles
- Compare different descending pathways, both by structure and function
- Explain the initiation of movement from the neurological connections
- Describe several reflex arcs and their functional roles

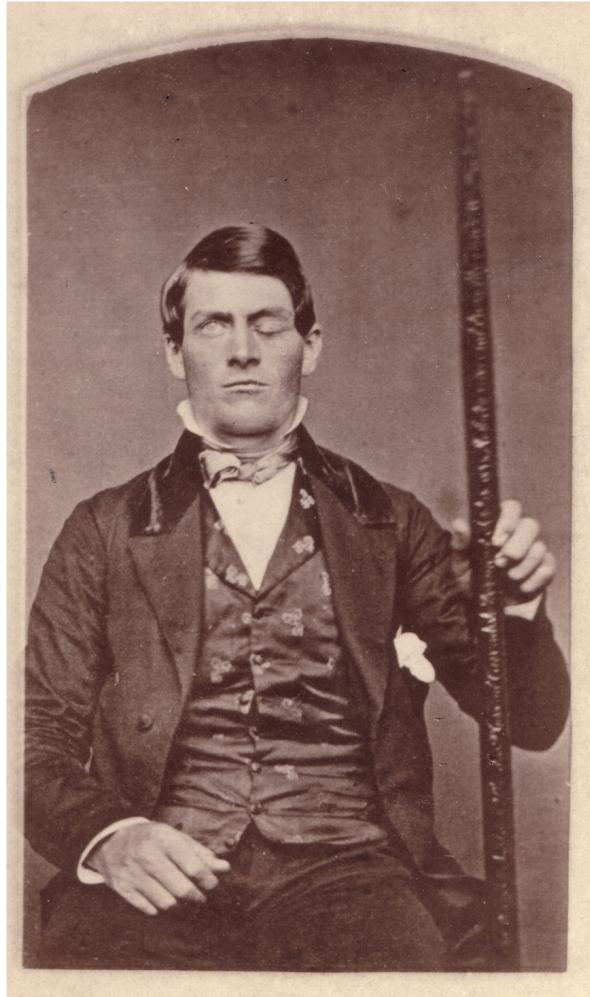
The defining characteristic of the somatic nervous system is that it controls skeletal muscles. Somatic senses inform the nervous system about the external environment, but the response to that is through voluntary muscle movement. The term “voluntary” suggests that there is a conscious decision to make a movement. However, some aspects of the somatic system use voluntary muscles without conscious control. One example is the ability of our breathing to switch to unconscious control while we are focused on another task. However, the muscles that are responsible for the basic process of breathing are also utilized for speech, which is entirely voluntary.

### Cortical Responses

Let’s start with sensory stimuli that have been registered through receptor cells and the information relayed to the CNS along ascending pathways. In the cerebral cortex, the initial processing of sensory perception progresses to associative processing and then integration in multimodal areas of cortex. These levels of processing can lead to the incorporation of sensory perceptions into memory, but more importantly, they lead to a response. The completion of cortical processing through the primary, associative, and integrative sensory areas initiates a similar progression of motor processing, usually in different cortical areas.

Whereas the sensory cortical areas are located in the occipital, temporal, and parietal lobes, motor functions are largely controlled by the frontal lobe (See [Figure 13.7](#)). The most anterior regions of the frontal lobe—the prefrontal areas—are important for **executive functions**, which are those cognitive functions that lead to goal-directed behaviors. These higher cognitive processes include **working memory**, which has been called a “mental scratch pad,” that can help organize and represent information that is not in the immediate environment. The prefrontal lobe is responsible for aspects of attention, such as inhibiting distracting thoughts and actions so that a person can focus on a goal and direct behavior toward achieving that goal.

The functions of the prefrontal cortex are integral to the personality of an individual, because it is largely responsible for what a person intends to do and how they accomplish those plans. A famous case of damage to the prefrontal cortex is that of Phineas Gage, dating back to 1848. He was a railroad worker who had a metal spike impale his prefrontal cortex ([Figure 14.27](#)). He survived the accident, but according to second-hand accounts, his personality changed drastically. Friends described him as no longer acting like himself. Whereas he was a hardworking, amiable man before the accident, he turned into an irritable, temperamental, and lazy man after the accident. Many of the accounts of his change may have been inflated in the retelling, and some behavior was likely attributable to alcohol used as a pain medication. However, the accounts suggest that some aspects of his personality did change. Also, there is new evidence that though his life changed dramatically, he was able to become a functioning stagecoach driver, suggesting that the brain has the ability to recover even from major trauma such as this.





**FIGURE 14.27 Phineas Gage** The victim of an accident while working on a railroad in 1848, Phineas Gage had a large iron rod impaled through the prefrontal cortex of his frontal lobe. After the accident, his personality appeared to change, but he eventually learned to cope with the trauma and lived as a coach driver even after such a traumatic event. (credit b: John M. Harlow, MD)

### Secondary Motor Cortices

In generating motor responses, the executive functions of the prefrontal cortex will need to initiate actual movements. One way to define the prefrontal area is any region of the frontal lobe that does not elicit movement when electrically stimulated. These are primarily in the anterior part of the frontal lobe. The regions of the frontal lobe that remain are the regions of the cortex that produce movement. The prefrontal areas project into the secondary motor cortices, which include the **premotor cortex** and the **supplemental motor area**.

Two important regions that assist in planning and coordinating movements are located adjacent to the primary motor cortex. The premotor cortex is more lateral, whereas the supplemental motor area is more medial and superior. The premotor area aids in controlling movements of the core muscles to maintain posture during movement, whereas the supplemental motor area is hypothesized to be responsible for planning and coordinating movement. The supplemental motor area also manages sequential movements that are based on prior experience (that is, learned movements). Neurons in these areas are most active leading up to the initiation of movement. For example, these areas might prepare the body for the movements necessary to drive a car in anticipation of a traffic light changing.

Adjacent to these two regions are two specialized motor planning centers. The **frontal eye fields** are responsible for moving the eyes in response to visual stimuli. There are direct connections between the frontal eye fields and the superior colliculus. Also, anterior to the premotor cortex and primary motor cortex is **Broca's area**. This area is responsible for controlling movements of the structures of speech production. The area is named after a French surgeon and anatomist who studied patients who could not produce speech. They did not have impairments to understanding speech, only to producing speech sounds, suggesting a damaged or underdeveloped Broca's area.

### Primary Motor Cortex

The primary motor cortex is located in the precentral gyrus of the frontal lobe. A neurosurgeon, Walter Penfield, described much of the basic understanding of the primary motor cortex by electrically stimulating the surface of the

cerebrum. Penfield would probe the surface of the cortex while the patient was only under local anesthesia so that he could observe responses to the stimulation. This led to the belief that the precentral gyrus directly stimulated muscle movement. We now know that the primary motor cortex receives input from several areas that aid in planning movement, and its principle output stimulates spinal cord neurons to stimulate skeletal muscle contraction.

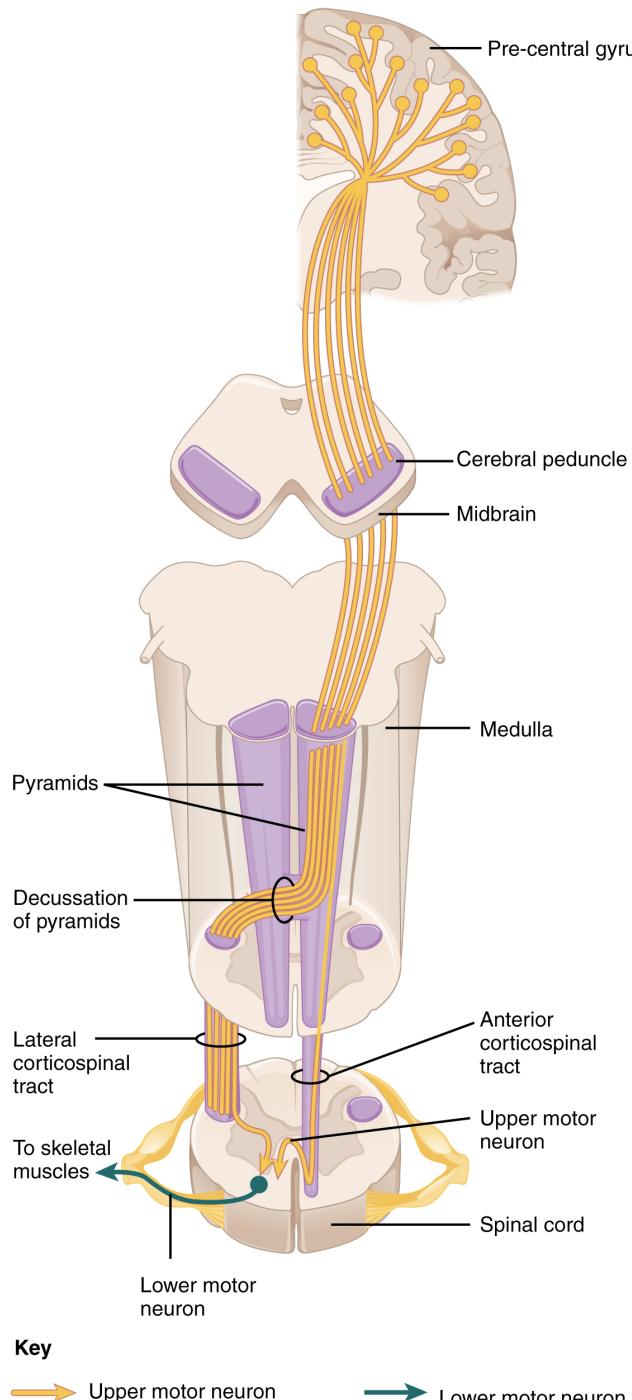
The primary motor cortex is arranged in a similar fashion to the primary somatosensory cortex, in that it has a topographical map of the body, creating a motor homunculus (see [Figure 14.23](#)). The neurons responsible for musculature in the feet and lower legs are in the medial wall of the precentral gyrus, with the thighs, trunk, and shoulder at the crest of the longitudinal fissure. The hand and face are in the lateral face of the gyrus. Also, the relative space allotted for the different regions is exaggerated in muscles that have greater innervation. The greatest amount of cortical space is given to muscles that perform fine, agile movements, such as the muscles of the fingers and the lower face. The “power muscles” that perform coarser movements, such as the buttock and back muscles, occupy much less space on the motor cortex.

### Descending Pathways

The motor output from the cortex descends into the brain stem and to the spinal cord to control the musculature through motor neurons. Neurons located in the primary motor cortex, named **Betz cells**, are large cortical neurons that synapse with lower motor neurons in the brain stem or in the spinal cord. The two descending pathways travelled by the axons of Betz cells are the **corticobulbar tract** and the **corticospinal tract**, respectively. Both tracts are named for their origin in the cortex and their targets—either the brain stem (the term “bulbar” refers to the brain stem as the bulb, or enlargement, at the top of the spinal cord) or the spinal cord.

These two descending pathways are responsible for the conscious or voluntary movements of skeletal muscles. Any motor command from the primary motor cortex is sent down the axons of the Betz cells to activate lower motor neurons in either the cranial motor nuclei or in the ventral horn of the spinal cord. The axons of the corticobulbar tract are ipsilateral, meaning they project from the cortex to the motor nucleus on the same side of the nervous system. Conversely, the axons of the corticospinal tract are largely contralateral, meaning that they cross the midline of the brain stem or spinal cord and synapse on the opposite side of the body. Therefore, the right motor cortex of the cerebrum controls muscles on the left side of the body, and vice versa.

The corticospinal tract descends from the cortex through the deep white matter of the cerebrum. It then passes between the caudate nucleus and putamen of the basal nuclei as a bundle called the **internal capsule**. The tract then passes through the midbrain as the **cerebral peduncles**, after which it burrows through the pons. Upon entering the medulla, the tracts make up the large white matter tract referred to as the **pyramids** ([Figure 14.28](#)). The defining landmark of the medullary-spinal border is the **pyramidal decussation**, which is where most of the fibers in the corticospinal tract cross over to the opposite side of the brain. At this point, the tract separates into two parts, which have control over different domains of the musculature.



**FIGURE 14.28 Corticospinal Tract** The major descending tract that controls skeletal muscle movements is the corticospinal tract. It is composed of two neurons, the upper motor neuron and the lower motor neuron. The upper motor neuron has its cell body in the primary motor cortex of the frontal lobe and synapses on the lower motor neuron, which is in the ventral horn of the spinal cord and projects to the skeletal muscle in the periphery.

#### Appendicular Control

The **lateral corticospinal tract** is composed of the fibers that cross the midline at the pyramidal decussation (see Figure 14.28). The axons cross over from the anterior position of the pyramids in the medulla to the lateral column of the spinal cord. These axons are responsible for controlling appendicular muscles.

This influence over the appendicular muscles means that the lateral corticospinal tract is responsible for moving the muscles of the arms and legs. The ventral horn in both the lower cervical spinal cord and the lumbar spinal cord both have wider ventral horns, representing the greater number of muscles controlled by these motor neurons. The

**cervical enlargement** is particularly large because there is greater control over the fine musculature of the upper limbs, particularly of the fingers. The **lumbar enlargement** is not as significant in appearance because there is less fine motor control of the lower limbs.

### Axial Control

The **anterior corticospinal tract** is responsible for controlling the muscles of the body trunk (see [Figure 14.28](#)). These axons do not decussate in the medulla. Instead, they remain in an anterior position as they descend the brain stem and enter the spinal cord. These axons then travel to the spinal cord level at which they synapse with a lower motor neuron. Upon reaching the appropriate level, the axons decussate, entering the ventral horn on the opposite side of the spinal cord from which they entered. In the ventral horn, these axons synapse with their corresponding lower motor neurons. The lower motor neurons are located in the medial regions of the ventral horn, because they control the axial muscles of the trunk.

Because movements of the body trunk involve both sides of the body, the anterior corticospinal tract is not entirely contralateral. Some collateral branches of the tract will project into the ipsilateral ventral horn to control synergistic muscles on that side of the body, or to inhibit antagonistic muscles through interneurons within the ventral horn. Through the influence of both sides of the body, the anterior corticospinal tract can coordinate postural muscles in broad movements of the body. These coordinating axons in the anterior corticospinal tract are often considered bilateral, as they are both ipsilateral and contralateral.

### INTERACTIVE LINK

Watch this [video](http://openstax.org/l/motorpathway) (<http://openstax.org/l/motorpathway>) to learn more about the descending motor pathway for the somatic nervous system. The autonomic connections are mentioned, which are covered in another chapter. From this brief video, only some of the descending motor pathway of the somatic nervous system is described. Which division of the pathway is described and which division is left out?

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### Extrapyramidal Controls

Other descending connections between the brain and the spinal cord are called the **extrapyramidal system**. The name comes from the fact that this system is outside the corticospinal pathway, which includes the pyramids in the medulla. A few pathways originating from the brain stem contribute to this system.

The **tectospinal tract** projects from the midbrain to the spinal cord and is important for postural movements that are driven by the superior colliculus. The name of the tract comes from an alternate name for the superior colliculus, which is the tectum. The **reticulospinal tract** connects the reticular system, a diffuse region of gray matter in the brain stem, with the spinal cord. This tract influences trunk and proximal limb muscles related to posture and locomotion. The reticulospinal tract also contributes to muscle tone and influences autonomic functions. The **vestibulospinal tract** connects the brain stem nuclei of the vestibular system with the spinal cord. This allows posture, movement, and balance to be modulated on the basis of equilibrium information provided by the vestibular system.

The pathways of the extrapyramidal system are influenced by subcortical structures. For example, connections between the secondary motor cortices and the extrapyramidal system modulate spine and cranium movements. The basal nuclei, which are important for regulating movement initiated by the CNS, influence the extrapyramidal system as well as its thalamic feedback to the motor cortex.

The conscious movement of our muscles is more complicated than simply sending a single command from the precentral gyrus down to the proper motor neurons. During the movement of any body part, our muscles relay information back to the brain, and the brain is constantly sending “revised” instructions back to the muscles. The cerebellum is important in contributing to the motor system because it compares cerebral motor commands with proprioceptive feedback. The corticospinal fibers that project to the ventral horn of the spinal cord have branches that also synapse in the pons, which project to the cerebellum. Also, the proprioceptive sensations of the dorsal column system have a collateral projection to the medulla that projects to the cerebellum. These two streams of information are compared in the cerebellar cortex. Conflicts between the motor commands sent by the cerebrum and body position information provided by the proprioceptors cause the cerebellum to stimulate the **red nucleus** of the midbrain. The red nucleus then sends corrective commands to the spinal cord along the **rubrospinal tract**. The

name of this tract comes from the word for red that is seen in the English word “ruby.”

A good example of how the cerebellum corrects cerebral motor commands can be illustrated by walking in water. An original motor command from the cerebrum to walk will result in a highly coordinated set of learned movements. However, in water, the body cannot actually perform a typical walking movement as instructed. The cerebellum can alter the motor command, stimulating the leg muscles to take larger steps to overcome the water resistance. The cerebellum can make the necessary changes through the rubrospinal tract. Modulating the basic command to walk also relies on spinal reflexes, but the cerebellum is responsible for calculating the appropriate response. When the cerebellum does not work properly, coordination and balance are severely affected. The most dramatic example of this is during the overconsumption of alcohol. Alcohol inhibits the ability of the cerebellum to interpret proprioceptive feedback, making it more difficult to coordinate body movements, such as walking a straight line, or guide the movement of the hand to touch the tip of the nose.

### **INTERACTIVE LINK**

Visit this [site \(<http://openstax.org/l/NYTmotor>\)](http://openstax.org/l/NYTmotor) to read about an elderly woman who starts to lose the ability to control fine movements, such as speech and the movement of limbs. Many of the usual causes were ruled out. It was not a stroke, Parkinson’s disease, diabetes, or thyroid dysfunction. The next most obvious cause was medication, so her pharmacist had to be consulted. The side effect of a drug meant to help her sleep had resulted in changes in motor control. What regions of the nervous system are likely to be the focus of haloperidol side effects?

## Ventral Horn Output

The somatic nervous system provides output strictly to skeletal muscles. The lower motor neurons, which are responsible for the contraction of these muscles, are found in the ventral horn of the spinal cord. These large, multipolar neurons have a corona of dendrites surrounding the cell body and an axon that extends out of the ventral horn. This axon travels through the ventral nerve root to join the emerging spinal nerve. The axon is relatively long because it needs to reach muscles in the periphery of the body. The diameters of cell bodies may be on the order of hundreds of micrometers to support the long axon; some axons are a meter in length, such as the lumbar motor neurons that innervate muscles in the first digits of the feet.

The axons will also branch to innervate multiple muscle fibers. Together, the motor neuron and all the muscle fibers that it controls make up a motor unit. Motor units vary in size. Some may contain up to 1000 muscle fibers, such as in the quadriceps, or they may only have 10 fibers, such as in an extraocular muscle. The number of muscle fibers that are part of a motor unit corresponds to the precision of control of that muscle. Also, muscles that have finer motor control have more motor units connecting to them, and this requires a larger topographical field in the primary motor cortex.

Motor neuron axons connect to muscle fibers at a neuromuscular junction. This is a specialized synaptic structure at which multiple axon terminals synapse with the muscle fiber sarcolemma. The synaptic end bulbs of the motor neurons secrete acetylcholine, which binds to receptors on the sarcolemma. The binding of acetylcholine opens ligand-gated ion channels, increasing the movement of cations across the sarcolemma. This depolarizes the sarcolemma, initiating muscle contraction. Whereas other synapses result in graded potentials that must reach a threshold in the postsynaptic target, activity at the neuromuscular junction reliably leads to muscle fiber contraction with every nerve impulse received from a motor neuron. However, the strength of contraction and the number of fibers that contract can be affected by the frequency of the motor neuron impulses.

## Reflexes

This chapter began by introducing reflexes as an example of the basic elements of the somatic nervous system. Simple somatic reflexes do not include the higher centers discussed for conscious or voluntary aspects of movement. Reflexes can be spinal or cranial, depending on the nerves and central components that are involved. The example described at the beginning of the chapter involved heat and pain sensations from a hot stove causing withdrawal of the arm through a connection in the spinal cord that leads to contraction of the biceps brachii. The description of this withdrawal reflex was simplified, for the sake of the introduction, to emphasize the parts of the somatic nervous system. But to consider reflexes fully, more attention needs to be given to this example.

As you withdraw your hand from the stove, you do not want to slow that reflex down. As the biceps brachii contracts, the antagonistic triceps brachii needs to relax. Because the neuromuscular junction is strictly excitatory, the biceps will contract when the motor nerve is active. Skeletal muscles do not actively relax. Instead the motor neuron needs to “quiet down,” or be inhibited. In the hot-stove withdrawal reflex, this occurs through an interneuron in the spinal cord. The interneuron’s cell body is located in the dorsal horn of the spinal cord. The interneuron receives a synapse from the axon of the sensory neuron that detects that the hand is being burned. In response to this stimulation from the sensory neuron, the interneuron then inhibits the motor neuron that controls the triceps brachii. This is done by releasing a neurotransmitter or other signal that hyperpolarizes the motor neuron connected to the triceps brachii, making it less likely to initiate an action potential. With this motor neuron being inhibited, the triceps brachii relaxes. Without the antagonistic contraction, withdrawal from the hot stove is faster and keeps further tissue damage from occurring.

Another example of a withdrawal reflex occurs when you step on a painful stimulus, like a tack or a sharp rock. The nociceptors that are activated by the painful stimulus activate the motor neurons responsible for contraction of the tibialis anterior muscle. This causes dorsiflexion of the foot. An inhibitory interneuron, activated by a collateral branch of the nociceptor fiber, will inhibit the motor neurons of the gastrocnemius and soleus muscles to cancel plantar flexion. An important difference in this reflex is that plantar flexion is most likely in progress as the foot is pressing down onto the tack. Contraction of the tibialis anterior is not the most important aspect of the reflex, as continuation of plantar flexion will result in further damage from stepping onto the tack.

Another type of reflex is a **stretch reflex**. In this reflex, when a skeletal muscle is stretched, a muscle spindle receptor is activated. The axon from this receptor structure will cause direct contraction of the muscle. A collateral of the muscle spindle fiber will also inhibit the motor neuron of the antagonist muscles. The reflex helps to maintain muscles at a constant length. A common example of this reflex is the knee jerk that is elicited by a rubber hammer struck against the patellar ligament in a physical exam.

A specialized reflex to protect the surface of the eye is the **corneal reflex**, or the eye blink reflex. When the cornea is stimulated by a tactile stimulus, or even by bright light in a related reflex, blinking is initiated. The sensory component travels through the trigeminal nerve, which carries somatosensory information from the face, or through the optic nerve, if the stimulus is bright light. The motor response travels through the facial nerve and innervates the orbicularis oculi on the same side. This reflex is commonly tested during a physical exam using an air puff or a gentle touch of a cotton-tipped applicator.

### **INTERACTIVE LINK**

Watch this [video](http://openstax.org/l/reflexarc) (<http://openstax.org/l/reflexarc>) to learn more about the reflex arc of the corneal reflex. When the right cornea senses a tactile stimulus, what happens to the left eye? Explain your answer.

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### **INTERACTIVE LINK**

Watch this [video](http://openstax.org/l/newreflex) (<http://openstax.org/l/newreflex>) to learn more about newborn reflexes. Newborns have a set of reflexes that are expected to have been crucial to survival before the modern age. These reflexes disappear as the baby grows, as some of them may be unnecessary as they age. The video demonstrates a reflex called the Babinski reflex, in which the foot flexes dorsally and the toes splay out when the sole of the foot is lightly scratched. This is normal for newborns, but it is a sign of reduced myelination of the spinal tract in adults. Why would this reflex be a problem for an adult?

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## Key Terms

- alkaloid** substance, usually from a plant source, that is chemically basic with respect to pH and will stimulate bitter receptors
- amacrine cell** type of cell in the retina that connects to the bipolar cells near the outer synaptic layer and provides the basis for early image processing within the retina
- ampulla** in the ear, the structure at the base of a semicircular canal that contains the hair cells and cupula for transduction of rotational movement of the head
- anosmia** loss of the sense of smell; usually the result of physical disruption of the first cranial nerve
- anterior corticospinal tract** division of the corticospinal pathway that travels through the ventral (anterior) column of the spinal cord and controls axial musculature through the medial motor neurons in the ventral (anterior) horn
- aqueous humor** watery fluid that fills the anterior chamber containing the cornea, iris, ciliary body, and lens of the eye
- ascending pathway** fiber structure that relays sensory information from the periphery through the spinal cord and brain stem to other structures of the brain
- association area** region of cortex connected to a primary sensory cortical area that further processes the information to generate more complex sensory perceptions
- audition** sense of hearing
- auricle** fleshy external structure of the ear
- basilar membrane** in the ear, the floor of the cochlear duct on which the organ of Corti sits
- Betz cells** output cells of the primary motor cortex that cause musculature to move through synapses on cranial and spinal motor neurons
- binocular depth cues** indications of the distance of visual stimuli on the basis of slight differences in the images projected onto either retina
- bipolar cell** cell type in the retina that connects the photoreceptors to the RGCs
- Broca's area** region of the frontal lobe associated with the motor commands necessary for speech production
- capsaicin** molecule that activates nociceptors by interacting with a temperature-sensitive ion channel and is the basis for "hot" sensations in spicy food
- cerebral peduncles** segments of the descending motor pathway that make up the white matter of the ventral midbrain
- cervical enlargement** region of the ventral (anterior) horn of the spinal cord that has a larger population of motor neurons for the greater number of and finer control of muscles of the upper limb
- chemoreceptor** sensory receptor cell that is sensitive to chemical stimuli, such as in taste, smell, or pain
- chief sensory nucleus** component of the trigeminal nuclei that is found in the pons
- choroid** highly vascular tissue in the wall of the eye that supplies the outer retina with blood
- ciliary body** smooth muscle structure on the interior surface of the iris that controls the shape of the lens through the zonule fibers
- circadian rhythm** internal perception of the daily cycle of light and dark based on retinal activity related to sunlight
- cochlea** auditory portion of the inner ear containing structures to transduce sound stimuli
- cochlear duct** space within the auditory portion of the inner ear that contains the organ of Corti and is adjacent to the scala tympani and scala vestibuli on either side
- cone photoreceptor** one of the two types of retinal receptor cell that is specialized for color vision through the use of three photopigments distributed through three separate populations of cells
- contralateral** word meaning "on the opposite side," as in axons that cross the midline in a fiber tract
- cornea** fibrous covering of the anterior region of the eye that is transparent so that light can pass through it
- corneal reflex** protective response to stimulation of the cornea causing contraction of the orbicularis oculi muscle resulting in blinking of the eye
- corticobulbar tract** connection between the cortex and the brain stem responsible for generating movement
- corticospinal tract** connection between the cortex and the spinal cord responsible for generating movement
- cupula** specialized structure within the base of a semicircular canal that bends the stereocilia of hair cells when the head rotates by way of the relative movement of the enclosed fluid
- decussate** to cross the midline, as in fibers that project from one side of the body to the other
- dorsal column system** ascending tract of the spinal cord associated with fine touch and proprioceptive sensations
- dorsal stream** connections between cortical areas from the occipital to parietal lobes that are responsible for the perception of visual motion and guiding movement of the body in relation to that motion

**encapsulated ending** configuration of a sensory receptor neuron with dendrites surrounded by specialized structures to aid in transduction of a particular type of sensation, such as the lamellated corpuscles in the deep dermis and subcutaneous tissue

**equilibrium** sense of balance that includes sensations of position and movement of the head

**executive functions** cognitive processes of the prefrontal cortex that lead to directing goal-directed behavior, which is a precursor to executing motor commands

**external ear** structures on the lateral surface of the head, including the auricle and the ear canal back to the tympanic membrane

**exteroceptor** sensory receptor that is positioned to interpret stimuli from the external environment, such as photoreceptors in the eye or somatosensory receptors in the skin

**extraocular muscle** one of six muscles originating out of the bones of the orbit and inserting into the surface of the eye which are responsible for moving the eye

**extrapyramidal system** pathways between the brain and spinal cord that are separate from the corticospinal tract and are responsible for modulating the movements generated through that primary pathway

**fasciculus cuneatus** lateral division of the dorsal column system composed of fibers from sensory neurons in the upper body

**fasciculus gracilis** medial division of the dorsal column system composed of fibers from sensory neurons in the lower body

**fibrous tunic** outer layer of the eye primarily composed of connective tissue known as the sclera and cornea

**fovea** exact center of the retina at which visual stimuli are focused for maximal acuity, where the retina is thinnest, at which there is nothing but photoreceptors

**free nerve ending** configuration of a sensory receptor neuron with dendrites in the connective tissue of the organ, such as in the dermis of the skin, that are most often sensitive to chemical, thermal, and mechanical stimuli

**frontal eye fields** area of the prefrontal cortex responsible for moving the eyes to attend to visual stimuli

**general sense** any sensory system that is distributed throughout the body and incorporated into organs of multiple other systems, such as the walls of the digestive organs or the skin

**gustation** sense of taste

**gustatory receptor cells** sensory cells in the taste bud that transduce the chemical stimuli of gustation

**hair cells** mechanoreceptor cells found in the inner ear that transduce stimuli for the senses of hearing and balance

**incus** (also, anvil) ossicle of the middle ear that connects the malleus to the stapes

**inferior colliculus** last structure in the auditory brainstem pathway that projects to the thalamus and superior colliculus

**inferior oblique** extraocular muscle responsible for lateral rotation of the eye

**inferior rectus** extraocular muscle responsible for looking down

**inner ear** structure within the temporal bone that contains the sensory apparatus of hearing and balance

**inner segment** in the eye, the section of a photoreceptor that contains the nucleus and other major organelles for normal cellular functions

**inner synaptic layer** layer in the retina where bipolar cells connect to RGCs

**interaural intensity difference** cue used to aid sound localization in the horizontal plane that compares the relative loudness of sounds at the two ears, because the ear closer to the sound source will hear a slightly more intense sound

**interaural time difference** cue used to help with sound localization in the horizontal plane that compares the relative time of arrival of sounds at the two ears, because the ear closer to the sound source will receive the stimulus microseconds before the other ear

**internal capsule** segment of the descending motor pathway that passes between the caudate nucleus and the putamen

**interoceptor** sensory receptor that is positioned to interpret stimuli from internal organs, such as stretch receptors in the wall of blood vessels

**ipsilateral** word meaning on the same side, as in axons that do not cross the midline in a fiber tract

**iris** colored portion of the anterior eye that surrounds the pupil

**kinesthesia** sense of body movement based on sensations in skeletal muscles, tendons, joints, and the skin

**lacrimal duct** duct in the medial corner of the orbit that drains tears into the nasal cavity

**lacrimal gland** gland lateral to the orbit that produces tears to wash across the surface of the eye

**lateral corticospinal tract** division of the

- corticospinal pathway** that travels through the lateral column of the spinal cord and controls appendicular musculature through the lateral motor neurons in the ventral (anterior) horn
- lateral geniculate nucleus** thalamic target of the RGCs that projects to the visual cortex
- lateral rectus** extraocular muscle responsible for abduction of the eye
- lens** component of the eye that focuses light on the retina
- levator palpebrae superioris** muscle that causes elevation of the upper eyelid, controlled by fibers in the oculomotor nerve
- lumbar enlargement** region of the ventral (anterior) horn of the spinal cord that has a larger population of motor neurons for the greater number of muscles of the lower limb
- macula** enlargement at the base of a semicircular canal at which transduction of equilibrium stimuli takes place within the ampulla
- malleus** (also, hammer) ossicle that is directly attached to the tympanic membrane
- mechanoreceptor** receptor cell that transduces mechanical stimuli into an electrochemical signal
- medial geniculate nucleus** thalamic target of the auditory brain stem that projects to the auditory cortex
- medial lemniscus** fiber tract of the dorsal column system that extends from the nuclei gracilis and cuneatus to the thalamus, and decussates
- medial rectus** extraocular muscle responsible for adduction of the eye
- mesencephalic nucleus** component of the trigeminal nuclei that is found in the midbrain
- middle ear** space within the temporal bone between the ear canal and bony labyrinth where the ossicles amplify sound waves from the tympanic membrane to the oval window
- multimodal integration area** region of the cerebral cortex in which information from more than one sensory modality is processed to arrive at higher level cortical functions such as memory, learning, or cognition
- neural tunic** layer of the eye that contains nervous tissue, namely the retina
- nociceptor** receptor cell that senses pain stimuli
- nucleus cuneatus** medullary nucleus at which first-order neurons of the dorsal column system synapse specifically from the upper body and arms
- nucleus gracilis** medullary nucleus at which first-order neurons of the dorsal column system synapse specifically from the lower body and legs
- odorant molecules** volatile chemicals that bind to receptor proteins in olfactory neurons to stimulate the sense of smell
- olfaction** sense of smell
- olfactory bulb** central target of the first cranial nerve; located on the ventral surface of the frontal lobe in the cerebrum
- olfactory epithelium** region of the nasal epithelium where olfactory neurons are located
- olfactory sensory neuron** receptor cell of the olfactory system, sensitive to the chemical stimuli of smell, the axons of which compose the first cranial nerve
- opsin** protein that contains the photosensitive cofactor retinal for phototransduction
- optic chiasm** decussation point in the visual system at which medial retina fibers cross to the other side of the brain
- optic disc** spot on the retina at which RGC axons leave the eye and blood vessels of the inner retina pass
- optic nerve** second cranial nerve, which is responsible visual sensation
- optic tract** name for the fiber structure containing axons from the retina posterior to the optic chiasm representing their CNS location
- organ of Corti** structure in the cochlea in which hair cells transduce movements from sound waves into electrochemical signals
- osmoreceptor** receptor cell that senses differences in the concentrations of bodily fluids on the basis of osmotic pressure
- ossicles** three small bones in the middle ear
- otolith** layer of calcium carbonate crystals located on top of the otolithic membrane
- otolithic membrane** gelatinous substance in the utricle and saccule of the inner ear that contains calcium carbonate crystals and into which the stereocilia of hair cells are embedded
- outer segment** in the eye, the section of a photoreceptor that contains opsin molecules that transduce light stimuli
- outer synaptic layer** layer in the retina at which photoreceptors connect to bipolar cells
- oval window** membrane at the base of the cochlea where the stapes attaches, marking the beginning of the scala vestibuli
- palpebral conjunctiva** membrane attached to the inner surface of the eyelids that covers the anterior surface of the cornea
- papilla** for gustation, a bump-like projection on the surface of the tongue that contains taste buds
- photoisomerization** chemical change in the retinal molecule that alters the bonding so that it switches

from the 11-*cis*-retinal isomer to the all-*trans*-retinal isomer

**photon** individual “packet” of light

**photoreceptor** receptor cell specialized to respond to light stimuli

**premotor cortex** cortical area anterior to the primary motor cortex that is responsible for planning movements

**primary sensory cortex** region of the cerebral cortex that initially receives sensory input from an ascending pathway from the thalamus and begins the processing that will result in conscious perception of that modality

**proprioception** sense of position and movement of the body

**proprioceptor** receptor cell that senses changes in the position and kinesthetic aspects of the body

**pupil** open hole at the center of the iris that light passes through into the eye

**pyramidal decussation** location at which corticospinal tract fibers cross the midline and segregate into the anterior and lateral divisions of the pathway

**pyramids** segment of the descending motor pathway that travels in the anterior position of the medulla

**receptor cell** cell that transduces environmental stimuli into neural signals

**red nucleus** midbrain nucleus that sends corrective commands to the spinal cord along the rubrospinal tract, based on disparity between an original command and the sensory feedback from movement

**reticulospinal tract** extrapyramidal connections between the brain stem and spinal cord that modulate movement, contribute to posture, and regulate muscle tone

**retina** nervous tissue of the eye at which phototransduction takes place

**retinal** cofactor in an opsin molecule that undergoes a biochemical change when struck by a photon (pronounced with a stress on the last syllable)

**retinal ganglion cell (RGC)** neuron of the retina that projects along the second cranial nerve

**rhodopsin** photopigment molecule found in the rod photoreceptors

**rod photoreceptor** one of the two types of retinal receptor cell that is specialized for low-light vision

**round window** membrane that marks the end of the scala tympani

**rubrospinal tract** descending motor control pathway, originating in the red nucleus, that mediates control of the limbs on the basis of cerebellar processing

**saccule** structure of the inner ear responsible for

transducing linear acceleration in the vertical plane

**scala tympani** portion of the cochlea that extends from the apex to the round window

**scala vestibuli** portion of the cochlea that extends from the oval window to the apex

**sclera** white of the eye

**semicircular canals** structures within the inner ear responsible for transducing rotational movement information

**sensory homunculus** topographic representation of the body within the somatosensory cortex demonstrating the correspondence between neurons processing stimuli and sensitivity

**sensory modality** a particular system for interpreting and perceiving environmental stimuli by the nervous system

**solitary nucleus** medullar nucleus that receives taste information from the facial and glossopharyngeal nerves

**somatosensation** general sense associated with modalities lumped together as touch

**special sense** any sensory system associated with a specific organ structure, namely smell, taste, sight, hearing, and balance

**spinal trigeminal nucleus** component of the trigeminal nuclei that is found in the medulla

**spinothalamic tract** ascending tract of the spinal cord associated with pain and temperature sensations

**spiral ganglion** location of neuronal cell bodies that transmit auditory information along the eighth cranial nerve

**stapes** (also, stirrup) ossicle of the middle ear that is attached to the inner ear

**stereocilia** array of apical membrane extensions in a hair cell that transduce movements when they are bent

**stretch reflex** response to activation of the muscle spindle stretch receptor that causes contraction of the muscle to maintain a constant length

**submodality** specific sense within a broader major sense such as sweet as a part of the sense of taste, or color as a part of vision

**superior colliculus** structure in the midbrain that combines visual, auditory, and somatosensory input to coordinate spatial and topographic representations of the three sensory systems

**superior oblique** extraocular muscle responsible for medial rotation of the eye

**superior rectus** extraocular muscle responsible for looking up

**supplemental motor area** cortical area anterior to the primary motor cortex that is responsible for

- planning movements
- suprachiasmatic nucleus** hypothalamic target of the retina that helps to establish the circadian rhythm of the body on the basis of the presence or absence of daylight
- taste buds** structures within a papilla on the tongue that contain gustatory receptor cells
- tectorial membrane** component of the organ of Corti that lays over the hair cells, into which the stereocilia are embedded
- tectospinal tract** extrapyramidal connections between the superior colliculus and spinal cord
- thermoreceptor** sensory receptor specialized for temperature stimuli
- topographical** relating to positional information
- transduction** process of changing an environmental stimulus into the electrochemical signals of the nervous system
- trochlea** cartilaginous structure that acts like a pulley for the superior oblique muscle
- tympanic membrane** ear drum
- umami** taste submodality for sensitivity to the concentration of amino acids; also called the savory sense
- utricle** structure of the inner ear responsible for transducing linear acceleration in the horizontal plane
- vascular tunic** middle layer of the eye primarily composed of connective tissue with a rich blood supply
- ventral posterior nucleus** nucleus in the thalamus that is the target of gustatory sensations and projects to the cerebral cortex
- ventral stream** connections between cortical areas from the occipital lobe to the temporal lobe that are responsible for identification of visual stimuli
- vestibular ganglion** location of neuronal cell bodies that transmit equilibrium information along the eighth cranial nerve
- vestibular nuclei** targets of the vestibular component of the eighth cranial nerve
- vestibule** in the ear, the portion of the inner ear responsible for the sense of equilibrium
- vestibulo-ocular reflex (VOR)** reflex based on connections between the vestibular system and the cranial nerves of eye movements that ensures images are stabilized on the retina as the head and body move
- vestibulospinal tract** extrapyramidal connections between the vestibular nuclei in the brain stem and spinal cord that modulate movement and contribute to balance on the basis of the sense of equilibrium
- visceral sense** sense associated with the internal organs
- vision** special sense of sight based on transduction of light stimuli
- visual acuity** property of vision related to the sharpness of focus, which varies in relation to retinal position
- vitreous humor** viscous fluid that fills the posterior chamber of the eye
- working memory** function of the prefrontal cortex to maintain a representation of information that is not in the immediate environment
- zonule fibers** fibrous connections between the ciliary body and the lens

## Chapter Review

### 14.1 Sensory Perception

The senses are olfaction (smell), gustation (taste), somatosensation (sensations associated with the skin and body), audition (hearing), equilibrium (balance), and vision. With the exception of somatosensation, this list represents the special senses, or those systems of the body that are associated with specific organs such as the tongue or eye. Somatosensation belongs to the general senses, which are those sensory structures that are distributed throughout the body and in the walls of various organs. The special senses are all primarily part of the somatic nervous system in that they are consciously perceived through cerebral processes, though some special senses contribute to autonomic function. The general senses can be divided into somatosensation, which is commonly considered touch, but includes tactile, pressure, vibration, temperature, and pain perception. The general senses

also include the visceral senses, which are separate from the somatic nervous system function in that they do not normally rise to the level of conscious perception.

The cells that transduce sensory stimuli into the electrochemical signals of the nervous system are classified on the basis of structural or functional aspects of the cells. The structural classifications are either based on the anatomy of the cell that is interacting with the stimulus (free nerve endings, encapsulated endings, or specialized receptor cell), or where the cell is located relative to the stimulus (interoceptor, exteroceptor, proprioceptor). Thirdly, the functional classification is based on how the cell transduces the stimulus into a neural signal. Chemoreceptors respond to chemical stimuli and are the basis for olfaction and gustation. Related to chemoreceptors are osmoreceptors and nociceptors

for fluid balance and pain reception, respectively. Mechanoreceptors respond to mechanical stimuli and are the basis for most aspects of somatosensation, as well as being the basis of audition and equilibrium in the inner ear. Thermoreceptors are sensitive to temperature changes, and photoreceptors are sensitive to light energy.

The nerves that convey sensory information from the periphery to the CNS are either spinal nerves, connected to the spinal cord, or cranial nerves, connected to the brain. Spinal nerves have mixed populations of fibers; some are motor fibers and some are sensory. The sensory fibers connect to the spinal cord through the dorsal root, which is attached to the dorsal root ganglion. Sensory information from the body that is conveyed through spinal nerves will project to the opposite side of the brain to be processed by the cerebral cortex. The cranial nerves can be strictly sensory fibers, such as the olfactory, optic, and vestibulocochlear nerves, or mixed sensory and motor nerves, such as the trigeminal, facial, glossopharyngeal, and vagus nerves. The cranial nerves are connected to the same side of the brain from which the sensory information originates.

## 14.2 Central Processing

Sensory input to the brain enters through pathways that travel through either the spinal cord (for somatosensory input from the body) or the brain stem (for everything else, except the visual and olfactory systems) to reach the diencephalon. In the diencephalon, sensory pathways reach the thalamus. This is necessary for all sensory systems to reach the cerebral cortex, except for the olfactory system that is directly connected to the frontal and temporal lobes.

The two major tracts in the spinal cord, originating from sensory neurons in the dorsal root ganglia, are the dorsal column system and the spinothalamic tract. The major differences between the two are in the type of information that is relayed to the brain and where the tracts decussate. The dorsal column system primarily carries information about touch and proprioception and crosses the midline in the medulla. The spinothalamic tract is primarily responsible for pain and temperature sensation and crosses the midline in the spinal cord at the level at which it enters. The trigeminal nerve adds similar sensation information from the head to these pathways.

The auditory pathway passes through multiple nuclei in the brain stem in which additional information is extracted from the basic frequency stimuli processed by the cochlea. Sound localization is made possible

through the activity of these brain stem structures. The vestibular system enters the brain stem and influences activity in the cerebellum, spinal cord, and cerebral cortex.

The visual pathway segregates information from the two eyes so that one half of the visual field projects to the other side of the brain. Within visual cortical areas, the perception of the stimuli and their location is passed along two streams, one ventral and one dorsal. The ventral visual stream connects to structures in the temporal lobe that are important for long-term memory formation. The dorsal visual stream interacts with the somatosensory cortex in the parietal lobe, and together they can influence the activity in the frontal lobe to generate movements of the body in relation to visual information.

## 14.3 Motor Responses

The motor components of the somatic nervous system begin with the frontal lobe of the brain, where the prefrontal cortex is responsible for higher functions such as working memory. The integrative and associate functions of the prefrontal lobe feed into the secondary motor areas, which help plan movements. The premotor cortex and supplemental motor area then feed into the primary motor cortex that initiates movements. Large Betz cells project through the corticobulbar and corticospinal tracts to synapse on lower motor neurons in the brain stem and ventral horn of the spinal cord, respectively. These connections are responsible for generating movements of skeletal muscles.

The extrapyramidal system includes projections from the brain stem and higher centers that influence movement, mostly to maintain balance and posture, as well as to maintain muscle tone. The superior colliculus and red nucleus in the midbrain, the vestibular nuclei in the medulla, and the reticular formation throughout the brain stem each have tracts projecting to the spinal cord in this system. Descending input from the secondary motor cortices, basal nuclei, and cerebellum connect to the origins of these tracts in the brain stem.

All of these motor pathways project to the spinal cord to synapse with motor neurons in the ventral horn of the spinal cord. These lower motor neurons are the cells that connect to skeletal muscle and cause contractions. These neurons project through the spinal nerves to connect to the muscles at neuromuscular junctions. One motor neuron connects to multiple muscle fibers within a target muscle. The number of fibers that are innervated by a single motor neuron varies on the basis of the precision necessary for that

muscle and the amount of force necessary for that motor unit. The quadriceps, for example, have many fibers controlled by single motor neurons for powerful contractions that do not need to be precise. The extraocular muscles have only a small number of fibers controlled by each motor neuron because moving the eyes does not require much force, but needs to be very precise.

Reflexes are the simplest circuits within the somatic nervous system. A withdrawal reflex from a painful stimulus only requires the sensory fiber that enters the

spinal cord and the motor neuron that projects to a muscle. Antagonist and postural muscles can be coordinated with the withdrawal, making the connections more complex. The simple, single neuronal connection is the basis of somatic reflexes. The corneal reflex is contraction of the orbicularis oculi muscle to blink the eyelid when something touches the surface of the eye. Stretch reflexes maintain a constant length of muscles by causing a contraction of a muscle to compensate for a stretch that can be sensed by a specialized receptor called a muscle spindle.

## Interactive Link Questions

- Watch this [video](http://openstax.org/l/DanielleReed) (<http://openstax.org/l/DanielleReed>) to learn about Dr. Danielle Reed of the Monell Chemical Senses Center in Philadelphia, PA, who became interested in science at an early age because of her sensory experiences. She recognized that her sense of taste was unique compared with other people she knew. Now, she studies the genetic differences between people and their sensitivities to taste stimuli. In the video, there is a brief image of a person sticking out their tongue, which has been covered with a colored dye. This is how Dr. Reed is able to visualize and count papillae on the surface of the tongue. People fall into two large groups known as “tasters” and “non-tasters” on the basis of the density of papillae on their tongue, which also indicates the number of taste buds. Non-tasters can taste food, but they are not as sensitive to certain tastes, such as bitterness. Dr. Reed discovered that she is a non-taster, which explains why she perceived bitterness differently than other people she knew. Are you very sensitive to tastes? Can you see any similarities among the members of your family?
- Figure 14.9** The basilar membrane is the thin membrane that extends from the central core of the cochlea to the edge. What is anchored to this membrane so that they can be activated by movement of the fluids within the cochlea?
- Watch this [video](http://openstax.org/l/ear1) (<http://openstax.org/l/ear1>) to learn more about how the structures of the ear convert sound waves into a neural signal by moving the “hairs,” or stereocilia, of the cochlear duct. Specific locations along the length of the duct encode specific frequencies, or pitches. The brain interprets the meaning of the sounds we hear as music, speech, noise, etc. Which ear structures are responsible for the amplification and transfer of sound from the external ear to the inner ear?
- Watch this [animation](http://openstax.org/l/ear2) (<http://openstax.org/l/ear2>) to learn more about the inner ear and to see the cochlea unroll, with the base at the back of the image and the apex at the front. Specific wavelengths of sound cause specific regions of the basilar membrane to vibrate, much like the keys of a piano produce sound at different frequencies. Based on the animation, where do frequencies—from high to low pitches—cause activity in the hair cells within the cochlear duct?
- Watch this [video](http://openstax.org/l/occipital) (<http://openstax.org/l/occipital>) to learn more about a transverse section through the brain that depicts the visual pathway from the eye to the occipital cortex. The first half of the pathway is the projection from the RGCs through the optic nerve to the lateral geniculate nucleus in the thalamus on either side. This first fiber in the pathway synapses on a thalamic cell that then projects to the visual cortex in the occipital lobe where “seeing,” or visual perception, takes place. This video gives an abbreviated overview of the visual system by concentrating on the pathway from the eyes to the occipital lobe. The video makes the statement (at 0:45) that “specialized cells in the retina called ganglion cells convert the light rays into electrical signals.” What aspect of retinal processing is simplified by that statement? Explain your answer.

6. Watch this [video](http://openstax.org/l/l_3-D1) to learn more about how the brain perceives 3-D motion. Similar to how retinal disparity offers 3-D moviegoers a way to extract 3-D information from the two-dimensional visual field projected onto the retina, the brain can extract information about movement in space by comparing what the two eyes see. If movement of a visual stimulus is leftward in one eye and rightward in the opposite eye, the brain interprets this as movement toward (or away) from the face along the midline. If both eyes see an object moving in the same direction, but at different rates, what would that mean for spatial movement?
7. The inability to recognize people by their faces is a troublesome problem. It can be caused by trauma, or it may be inborn. Watch this [video](http://openstax.org/l/faces) to learn more about a person who lost the ability to recognize faces as the result of an injury. She cannot recognize the faces of close family members or herself. What other information can a person suffering from prosopagnosia use to figure out whom they are seeing?
8. Watch this [video](http://openstax.org/l/motorpathway) to learn more about the descending motor pathway for the somatic nervous system. The autonomic connections are mentioned, which are covered in another chapter. From this brief video, only some of the descending motor pathway of the somatic nervous system is described. Which division of the pathway is described and which division is left out?
9. Visit this [site](http://openstax.org/l/NYTmotor) to read about an elderly woman who starts to lose the ability to control fine movements, such as speech and the movement of limbs. Many of the usual causes were ruled out. It was not a stroke, Parkinson's disease, diabetes, or thyroid dysfunction. The next most obvious cause was medication, so her pharmacist had to be consulted. The side effect of a drug meant to help her sleep had resulted in changes in motor control. What regions of the nervous system are likely to be the focus of haloperidol side effects?
10. Watch this [video](http://openstax.org/l/reflexarc) to learn more about the reflex arc of the corneal reflex. When the right cornea senses a tactile stimulus, what happens to the left eye? Explain your answer.
11. Watch this [video](http://openstax.org/l/newreflex) to learn more about newborn reflexes. Newborns have a set of reflexes that are expected to have been crucial to survival before the modern age. These reflexes disappear as the baby grows, as some of them may be unnecessary as they age. The video demonstrates a reflex called the Babinski reflex, in which the foot flexes dorsally and the toes splay out when the sole of the foot is lightly scratched. This is normal for newborns, but it is a sign of reduced myelination of the spinal tract in adults. Why would this reflex be a problem for an adult?

## Review Questions

12. What type of receptor cell is responsible for transducing pain stimuli?
  - a. mechanoreceptor
  - b. nociceptor
  - c. osmoreceptor
  - d. photoreceptor
13. Which of these cranial nerves is part of the gustatory system?
  - a. olfactory
  - b. trochlear
  - c. trigeminal
  - d. facial
14. Which submodality of taste is sensitive to the pH of saliva?
  - a. umami
  - b. sour
  - c. bitter
  - d. sweet
15. Axons from which neuron in the retina make up the optic nerve?
  - a. amacrine cells
  - b. photoreceptors
  - c. bipolar cells
  - d. retinal ganglion cells

- 16.** What type of receptor cell is involved in the sensations of sound and balance?
- photoreceptor
  - chemoreceptor
  - mechanoreceptor
  - nociceptor
- 17.** Which of these sensory modalities does *not* pass through the ventral posterior thalamus?
- gustatory
  - proprioception
  - audition
  - nociception
- 18.** Which nucleus in the medulla is connected to the inferior colliculus?
- solitary nucleus
  - vestibular nucleus
  - chief sensory nucleus
  - cochlear nucleus
- 19.** Visual stimuli in the upper-left visual field will be processed in what region of the primary visual cortex?
- inferior right
  - inferior left
  - superior right
  - superior left
- 20.** Which location on the body has the largest region of somatosensory cortex representing it, according to the sensory homunculus?
- lips
  - thigh
  - elbow
  - neck
- 21.** Which of the following is a direct target of the vestibular ganglion?
- superior colliculus
  - cerebellum
  - thalamus
  - optic chiasm
- 22.** Which region of the frontal lobe is responsible for initiating movement by directly connecting to cranial and spinal motor neurons?
- prefrontal cortex
  - supplemental motor area
  - premotor cortex
  - primary motor cortex
- 23.** Which extrapyramidal tract incorporates equilibrium sensations with motor commands to aid in posture and movement?
- tectospinal tract
  - vestibulospinal tract
  - reticulospinal tract
  - corticospinal tract
- 24.** Which region of gray matter in the spinal cord contains motor neurons that innervate skeletal muscles?
- ventral horn
  - dorsal horn
  - lateral horn
  - lateral column
- 25.** What type of reflex can protect the foot when a painful stimulus is sensed?
- stretch reflex
  - gag reflex
  - withdrawal reflex
  - corneal reflex
- 26.** What is the name for the topographical representation of the sensory input to the somatosensory cortex?
- homunculus
  - homo sapiens
  - postcentral gyrus
  - primary cortex

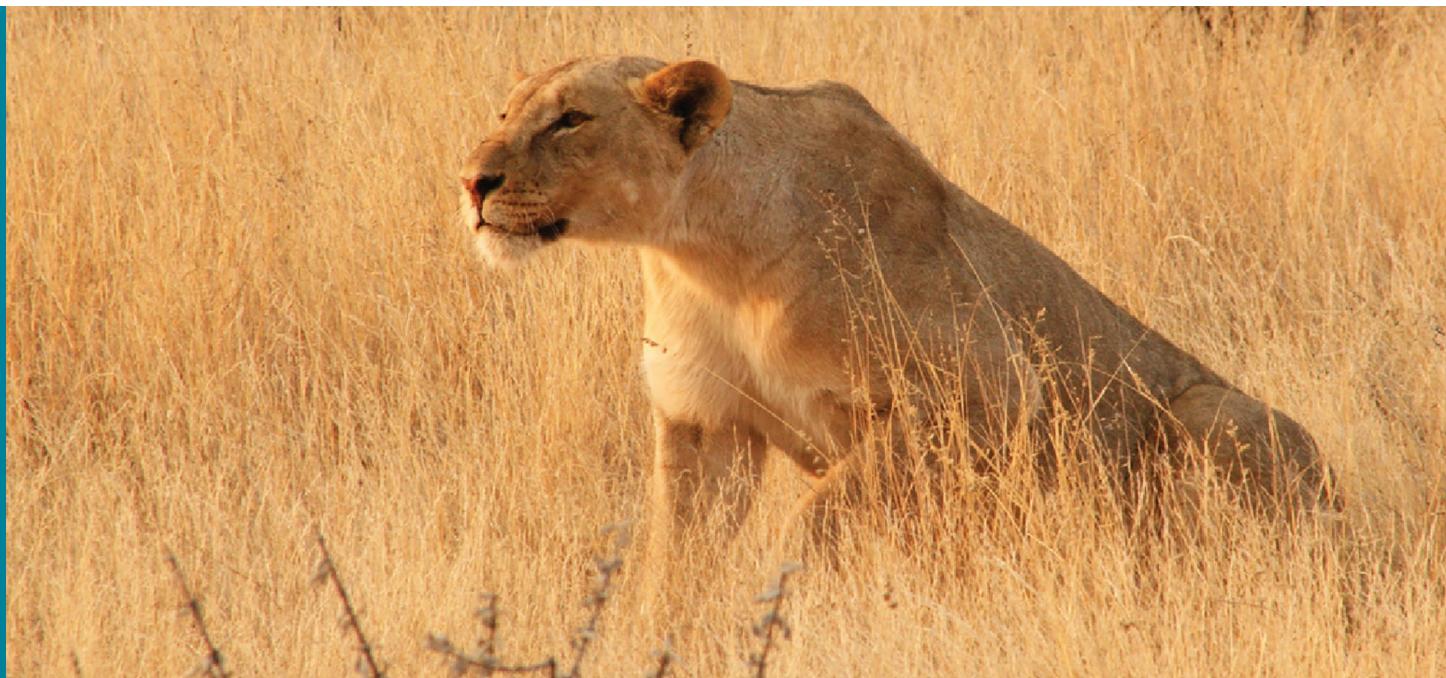
## Critical Thinking Questions

- 27.** The sweetener known as stevia can replace glucose in food. What does the molecular similarity of stevia to glucose mean for the gustatory sense?
- 28.** Why does the blind spot from the optic disc in either eye not result in a blind spot in the visual field?
- 29.** Following a motorcycle accident, the victim loses the ability to move the right leg but has normal control over the left one, suggesting a hemisection somewhere in the thoracic region of the spinal cord. What sensory deficits would be expected in terms of touch versus pain? Explain your answer.
- 30.** A pituitary tumor can cause perceptual losses in the lateral visual field. The pituitary gland is located directly inferior to the hypothalamus. Why would this happen?

- 31.** The prefrontal lobotomy is a drastic—and largely out-of-practice—procedure used to disconnect that portion of the cerebral cortex from the rest of the frontal lobe and the diencephalon as a psychiatric therapy. Why would this have been thought necessary for someone with a potentially uncontrollable behavior?
- 32.** If a reflex is a limited circuit within the somatic system, why do physical and neurological exams include them to test the health of an individual?

# CHAPTER 15

## The Autonomic Nervous System



**Figure 15.1 Fight or Flight?** Though the threats that modern humans face are not large predators, the autonomic nervous system is adapted to this type of stimulus. The modern world presents stimuli that trigger the same response. (credit: Vernon Swanepoel)

### CHAPTER OBJECTIVES

After studying this chapter, you will be able to:

- Describe the components of the autonomic nervous system
- Differentiate between the structures of the sympathetic and parasympathetic divisions in the autonomic nervous system
- Name the components of a visceral reflex specific to the autonomic division to which it belongs
- Predict the response of a target effector to autonomic input on the basis of the released signaling molecule
- Describe how the central nervous system coordinates and contributes to autonomic functions

**INTRODUCTION** The autonomic nervous system is often associated with the “fight-or-flight response,” which refers to the preparation of the body to either run away from a threat or to stand and fight in the face of that threat. To suggest what this means, consider the (very unlikely) situation of seeing a lioness hunting out on the savannah. Though this is not a common threat that humans deal with in the modern world, it represents the type of environment in which the human species thrived and adapted. The spread of humans around the world to the present state of the modern age occurred much more quickly than any species would adapt to environmental pressures such as predators. However, the reactions modern humans have in the modern world are based on these prehistoric situations. If your boss is walking down the hallway on Friday afternoon looking for “volunteers” to come in on the weekend, your response is the same as the prehistoric human seeing the lioness running across the savannah: fight or flight.

Most likely, your response to your boss—not to mention the lioness—would be flight. Run away! The autonomic system is responsible for the physiological response to make that possible, and hopefully successful. Adrenaline starts to flood your circulatory system. Your heart rate increases. Sweat glands become active. The bronchi of the lungs dilate to allow more air exchange. Pupils dilate to increase visual information. Blood pressure increases in general, and blood vessels dilate in skeletal muscles. Time to run. Similar physiological responses would occur in preparation for fighting off the threat.

This response should sound a bit familiar. The autonomic nervous system is tied into emotional responses as well,

and the fight-or-flight response probably sounds like a panic attack. In the modern world, these sorts of reactions are associated with anxiety as much as with response to a threat. It is engrained in the nervous system to respond like this. In fact, the adaptations of the autonomic nervous system probably predate the human species and are likely to be common to all mammals, and perhaps shared by many animals. That lioness might herself be threatened in some other situation.

However, the autonomic nervous system is not just about responding to threats. Besides the fight-or-flight response, there are the responses referred to as “rest and digest.” If that lioness is successful in her hunting, then she is going to rest from the exertion. Her heart rate will slow. Breathing will return to normal. The digestive system has a big job to do. Much of the function of the autonomic system is based on the connections within an autonomic, or visceral, reflex.

## 15.1 Divisions of the Autonomic Nervous System

### LEARNING OBJECTIVES

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

- Name the components that generate the sympathetic and parasympathetic responses of the autonomic nervous system
- Explain the differences in output connections within the two divisions of the autonomic nervous system
- Describe the signaling molecules and receptor proteins involved in communication within the two divisions of the autonomic nervous system

The nervous system can be divided into two functional parts: the somatic nervous system and the autonomic nervous system. The major differences between the two systems are evident in the responses that each produces. The somatic nervous system causes contraction of skeletal muscles. The autonomic nervous system controls cardiac and smooth muscle, as well as glandular tissue. The somatic nervous system is associated with voluntary responses (though many can happen without conscious awareness, like breathing), and the autonomic nervous system is associated with involuntary responses, such as those related to homeostasis.

The autonomic nervous system regulates many of the internal organs through a balance of two aspects, or divisions. In addition to the endocrine system, the autonomic nervous system is instrumental in homeostatic mechanisms in the body. The two divisions of the autonomic nervous system are the **sympathetic division** and the **parasympathetic division**. The sympathetic system is associated with the **fight-or-flight response**, and parasympathetic activity is referred to by the epithet of **rest and digest**. Homeostasis is the balance between the two systems. At each target effector, dual innervation determines activity. For example, the heart receives connections from both the sympathetic and parasympathetic divisions. One causes heart rate to increase, whereas the other causes heart rate to decrease.

### INTERACTIVE LINK

Watch this [video \(<http://openstax.org/l/fightflight>\)](http://openstax.org/l/fightflight) to learn more about adrenaline and the fight-or-flight response. When someone is said to have a rush of adrenaline, the image of bungee jumpers or skydivers usually comes to mind. But adrenaline, also known as epinephrine, is an important chemical in coordinating the body’s fight-or-flight response. In this video, you look inside the physiology of the fight-or-flight response, as envisioned for a firefighter. His body’s reaction is the result of the sympathetic division of the autonomic nervous system causing system-wide changes as it prepares for extreme responses. What two changes does adrenaline bring about to help the skeletal muscle response?

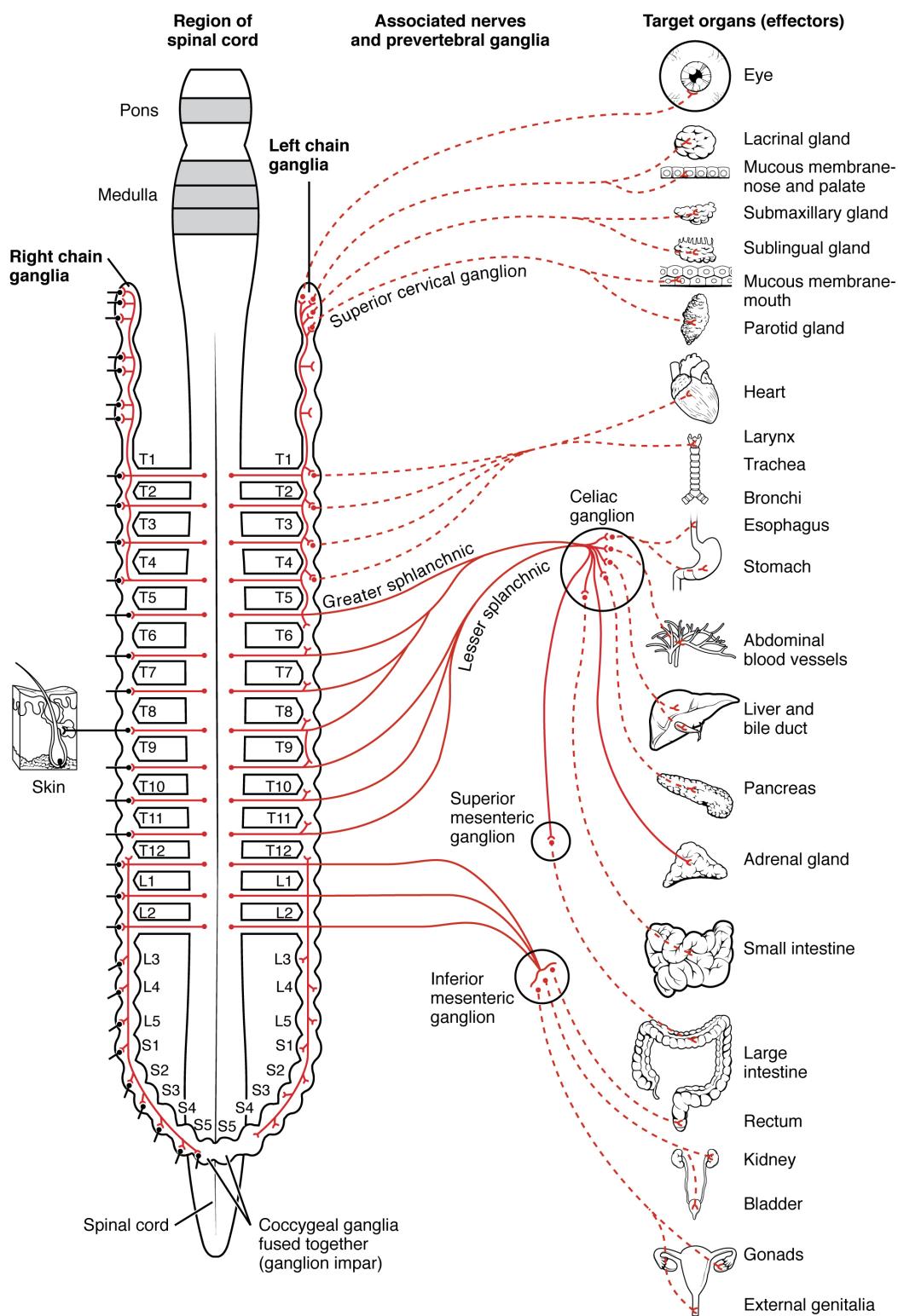
### Sympathetic Division of the Autonomic Nervous System

To respond to a threat—to fight or to run away—the sympathetic system causes divergent effects as many different effector organs are activated together for a common purpose. More oxygen needs to be inhaled and delivered to skeletal muscle. The respiratory, cardiovascular, and musculoskeletal systems are all activated together. Additionally, sweating keeps the excess heat that comes from muscle contraction from causing the body to overheat. The digestive system shuts down so that blood is not absorbing nutrients when it should be delivering oxygen to skeletal muscles. To coordinate all these responses, the connections in the sympathetic system diverge

from a limited region of the central nervous system (CNS) to a wide array of ganglia that project to the many effector organs simultaneously. The complex set of structures that compose the output of the sympathetic system make it possible for these disparate effectors to come together in a coordinated, systemic change.

The sympathetic division of the autonomic nervous system influences the various organ systems of the body through connections emerging from the thoracic and upper lumbar spinal cord. It is referred to as the **thoracolumbar system** to reflect this anatomical basis. A **central neuron** in the lateral horn of any of these spinal regions projects to ganglia adjacent to the vertebral column through the ventral spinal roots. The majority of ganglia of the sympathetic system belong to a network of **sympathetic chain ganglia** that runs alongside the vertebral column. The ganglia appear as a series of clusters of neurons linked by axonal bridges. There are typically 23 ganglia in the chain on either side of the spinal column. Three correspond to the cervical region, 12 are in the thoracic region, four are in the lumbar region, and four correspond to the sacral region. The cervical and sacral levels are not connected to the spinal cord directly through the spinal roots, but through ascending or descending connections through the bridges within the chain.

A diagram that shows the connections of the sympathetic system is somewhat like a circuit diagram that shows the electrical connections between different receptacles and devices. In [Figure 15.2](#), the “circuits” of the sympathetic system are intentionally simplified.



**FIGURE 15.2 Connections of Sympathetic Division of the Autonomic Nervous System** Neurons from the lateral horn of the spinal cord (preganglionic nerve fibers - solid lines) project to the chain ganglia on either side of the vertebral column or to collateral (prevertebral) ganglia that are anterior to the vertebral column in the abdominal cavity. Axons from these ganglionic neurons (postganglionic nerve fibers - dotted lines) then project to target effectors throughout the body.

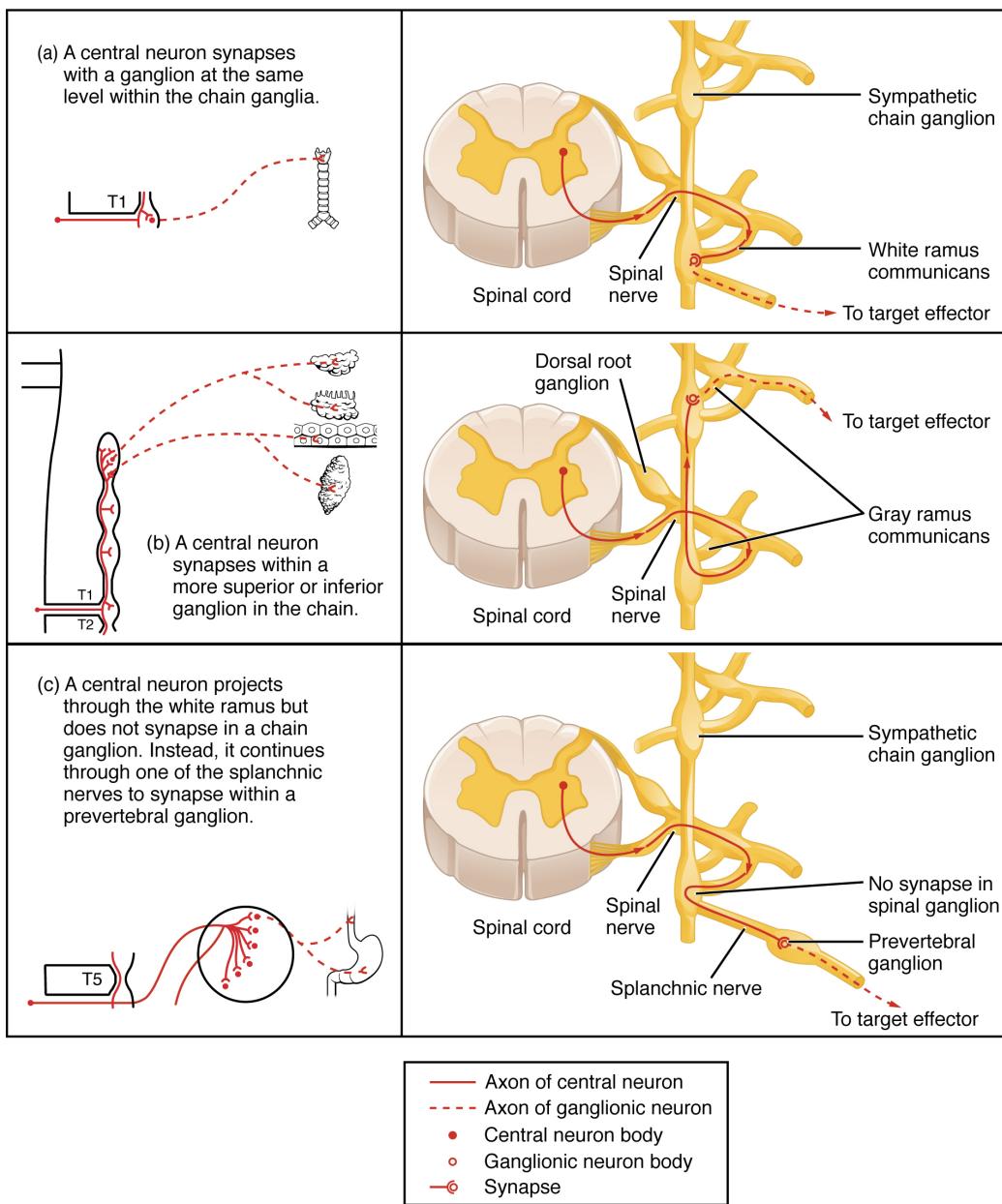
To continue with the analogy of the circuit diagram, there are three different types of “junctions” that operate within the sympathetic system (Figure 15.3). The first type is most direct: the sympathetic nerve projects to the chain ganglion at the same level as the **target effector** (the organ, tissue, or gland to be innervated). An example of this type is spinal nerve T1 that synapses with the T1 chain ganglion to innervate the trachea. The fibers of this branch

are called **white rami communicantes** (singular = ramus communicans); they are myelinated and therefore referred to as white (see [Figure 15.3a](#)). The axon from the central neuron (the preganglionic fiber shown as a solid line) synapses with the **ganglionic neuron** (with the postganglionic fiber shown as a dashed line). This neuron then projects to a target effector—in this case, the trachea—via **gray rami communicantes**, which are unmyelinated axons.

In some cases, the target effectors are located superior or inferior to the spinal segment at which the preganglionic fiber emerges. With respect to the “wiring” involved, the synapse with the ganglionic neuron occurs at chain ganglia superior or inferior to the location of the central neuron. An example of this is spinal nerve T1 that innervates the eye. The spinal nerve tracks up through the chain until it reaches the **superior cervical ganglion**, where it synapses with the postganglionic neuron (see [Figure 15.3b](#)). The cervical ganglia are referred to as **paravertebral ganglia**, given their location adjacent to prevertebral ganglia in the sympathetic chain.

Not all axons from the central neurons terminate in the chain ganglia. Additional branches from the ventral nerve root continue through the chain and on to one of the collateral ganglia as the **greater splanchnic nerve** or **lesser splanchnic nerve**. For example, the greater splanchnic nerve at the level of T5 synapses with a collateral ganglion outside the chain before making the connection to the postganglionic nerves that innervate the stomach (see [Figure 15.3c](#)).

**Collateral ganglia**, also called **prevertebral ganglia**, are situated anterior to the vertebral column and receive inputs from splanchnic nerves as well as central sympathetic neurons. They are associated with controlling organs in the abdominal cavity, and are also considered part of the enteric nervous system. The three collateral ganglia are the **celiac ganglion**, the **superior mesenteric ganglion**, and the **inferior mesenteric ganglion** (see [Figure 15.2](#)). The word celiac is derived from the Latin word “coelom,” which refers to a body cavity (in this case, the abdominal cavity), and the word mesenteric refers to the digestive system.



**FIGURE 15.3 Sympathetic Connections and Chain Ganglia** The axon from a central sympathetic neuron in the spinal cord can project to the periphery in a number of different ways. (a) The fiber can project out to the ganglion at the same level and synapse on a ganglionic neuron. (b) A branch can project to more superior or inferior ganglion in the chain. (c) A branch can project through the white ramus communicans, but not terminate on a ganglionic neuron in the chain. Instead, it projects through one of the splanchnic nerves to a collateral ganglion or the adrenal medulla (not pictured).

An axon from the central neuron that projects to a sympathetic ganglion is referred to as a **preganglionic fiber** or **neuron**, and represents the output from the CNS to the ganglion. Because the sympathetic ganglia are adjacent to the vertebral column, preganglionic sympathetic fibers are relatively short, and they are myelinated. A **postganglionic fiber**—the axon from a ganglionic neuron that projects to the target effector—represents the output of a ganglion that directly influences the organ. Compared with the preganglionic fibers, postganglionic sympathetic fibers are long because of the relatively greater distance from the ganglion to the target effector. These fibers are unmyelinated. (Note that the term “postganglionic neuron” may be used to describe the projection from a ganglion to the target. The problem with that usage is that the cell body is in the ganglion, and only the fiber is postganglionic. Typically, the term neuron applies to the entire cell.)

One type of preganglionic sympathetic fiber does not terminate in a ganglion. These are the axons from central sympathetic neurons that project to the **adrenal medulla**, the interior portion of the adrenal gland. These axons are

still referred to as preganglionic fibers, but the target is not a ganglion. The adrenal medulla releases signaling molecules into the bloodstream, rather than using axons to communicate with target structures. The cells in the adrenal medulla that are contacted by the preganglionic fibers are called **chromaffin cells**. These cells are neurosecretory cells that develop from the neural crest along with the sympathetic ganglia, reinforcing the idea that the gland is, functionally, a sympathetic ganglion.

The projections of the sympathetic division of the autonomic nervous system diverge widely, resulting in a broad influence of the system throughout the body. As a response to a threat, the sympathetic system would increase heart rate and breathing rate and cause blood flow to the skeletal muscle to increase and blood flow to the digestive system to decrease. Sweat gland secretion should also increase as part of an integrated response. All of those physiological changes are going to be required to occur together to run away from the hunting lioness, or the modern equivalent. This divergence is seen in the branching patterns of preganglionic sympathetic neurons—a single preganglionic sympathetic neuron may have 10–20 targets. An axon that leaves a central neuron of the lateral horn in the thoracolumbar spinal cord will pass through the white ramus communicans and enter the sympathetic chain, where it will branch toward a variety of targets. At the level of the spinal cord at which the preganglionic sympathetic fiber exits the spinal cord, a branch will synapse on a neuron in the adjacent chain ganglion. Some branches will extend up or down to a different level of the chain ganglia. Other branches will pass through the chain ganglia and project through one of the splanchnic nerves to a collateral ganglion. Finally, some branches may project through the splanchnic nerves to the adrenal medulla. All of these branches mean that one preganglionic neuron can influence different regions of the sympathetic system very broadly, by acting on widely distributed organs.

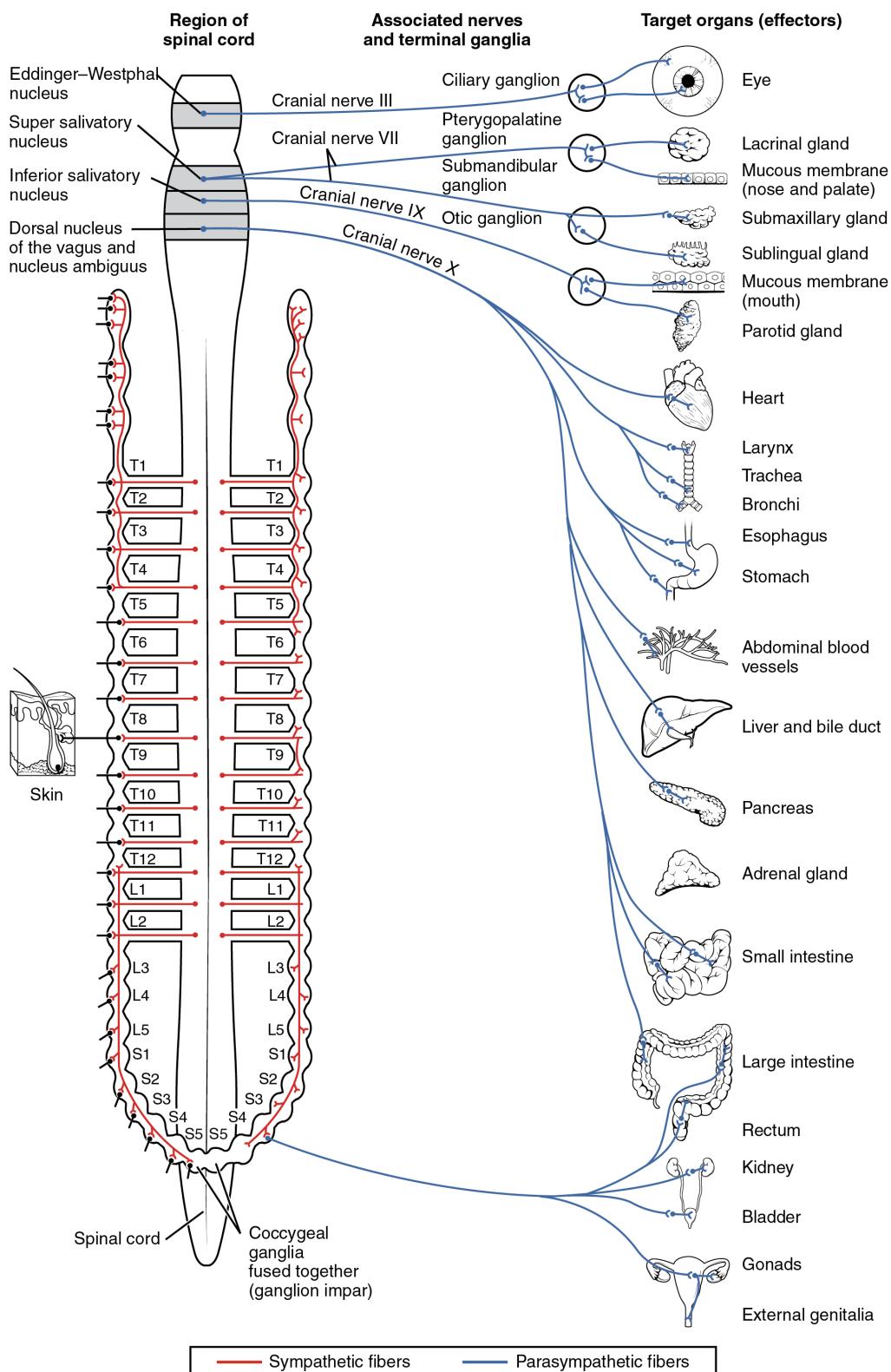
### Parasympathetic Division of the Autonomic Nervous System

The parasympathetic system can also be referred to as the **craniosacral system** (or outflow) because the preganglionic neurons are located in nuclei of the brain stem and the lateral horn of the sacral spinal cord.

The connections, or “circuits,” of the parasympathetic division are similar to the general layout of the sympathetic division with a few specific differences ([Figure 15.4](#)). The preganglionic fibers from the cranial region travel in cranial nerves, whereas preganglionic fibers from the sacral region travel in spinal nerves. The targets of these fibers are **terminal ganglia**, which are located near—or even within—the target effector. These ganglia are often referred to as **intramural ganglia** when they are found within the walls of the target organ. The postganglionic fiber projects from the terminal ganglia a short distance to the target effector, or to the specific target tissue within the organ.

Comparing the relative lengths of axons in the parasympathetic system, the preganglionic fibers are long and the postganglionic fibers are short because the ganglia are close to—and sometimes within—the target effectors.

The cranial component of the parasympathetic system is based in particular nuclei of the brain stem. In the midbrain, the **Edinger-Westphal nucleus** is part of the oculomotor complex, and axons from those neurons travel with the fibers in the oculomotor nerve (cranial nerve III) that innervate the extraocular muscles. The preganglionic parasympathetic fibers within cranial nerve III terminate in the **ciliary ganglion**, which is located in the posterior orbit. The postganglionic parasympathetic fibers then project to the smooth muscle of the iris to control pupillary size. In the upper medulla, the salivatory nuclei contain neurons with axons that project through the facial and glossopharyngeal nerves to ganglia that control salivary glands. Tear production is influenced by parasympathetic fibers in the facial nerve, which activate a ganglion, and ultimately the lacrimal (tear) gland. Neurons in the **dorsal nucleus of the vagus nerve** and the **nucleus ambiguus** project through the vagus nerve (cranial nerve X) to the terminal ganglia of the thoracic and abdominal cavities. Parasympathetic preganglionic fibers primarily influence the heart, bronchi, and esophagus in the thoracic cavity and the stomach, liver, pancreas, gall bladder, and small intestine of the abdominal cavity. The postganglionic fibers from the ganglia activated by the vagus nerve are often incorporated into the structure of the organ, such as the **mesenteric plexus** of the digestive tract organs and the intramural ganglia.



**FIGURE 15.4 Connections of Parasympathetic Division of the Autonomic Nervous System** Neurons from brain-stem nuclei, or from the lateral horn of the sacral spinal cord, project to terminal ganglia near or within the various organs of the body. Axons from these ganglionic neurons then project the short distance to those target effectors.

## Chemical Signaling in the Autonomic Nervous System

Where an autonomic neuron connects with a target, there is a synapse. The electrical signal of the action potential

causes the release of a signaling molecule, which will bind to receptor proteins on the target cell. Synapses of the autonomic system are classified as either **cholinergic**, meaning that **acetylcholine (ACh)** is released, or **adrenergic**, meaning that **norepinephrine** is released. The terms cholinergic and adrenergic refer not only to the signaling molecule that is released but also to the class of receptors that each binds.

The cholinergic system includes two classes of receptor: the **nicotinic receptor** and the **muscarinic receptor**. Both receptor types bind to ACh and cause changes in the target cell. The nicotinic receptor is a **ligand-gated cation channel** and the muscarinic receptor is a **G protein-coupled receptor**. The receptors are named for, and differentiated by, other molecules that bind to them. Whereas nicotine will bind to the nicotinic receptor, and muscarine will bind to the muscarinic receptor, there is no cross-reactivity between the receptors. The situation is similar to locks and keys. Imagine two locks—one for a classroom and the other for an office—that are opened by two separate keys. The classroom key will not open the office door and the office key will not open the classroom door. This is similar to the specificity of nicotine and muscarine for their receptors. However, a master key can open multiple locks, such as a master key for the Biology Department that opens both the classroom and the office doors. This is similar to ACh that binds to both types of receptors. The molecules that define these receptors are not crucial—they are simply tools for researchers to use in the laboratory. These molecules are **exogenous**, meaning that they are made outside of the human body, so a researcher can use them without any confounding **endogenous** results (results caused by the molecules produced in the body).

The adrenergic system also has two types of receptors, named the **alpha ( $\alpha$ )-adrenergic receptor** and **beta ( $\beta$ )-adrenergic receptor**. Unlike cholinergic receptors, these receptor types are not classified by which drugs can bind to them. All of them are G protein-coupled receptors. There are two types of  $\alpha$ -adrenergic receptors, termed  $\alpha_1$ , and  $\alpha_2$ , and there are three types of  $\beta$ -adrenergic receptors, termed  $\beta_1$ ,  $\beta_2$  and  $\beta_3$ . An additional aspect of the adrenergic system is that there is a second signaling molecule called **epinephrine**. The chemical difference between norepinephrine and epinephrine is the addition of a methyl group ( $\text{CH}_3$ ) in epinephrine. The prefix “nor-” actually refers to this chemical difference, in which a methyl group is missing.

The term adrenergic should remind you of the word adrenaline, which is associated with the fight-or-flight response described at the beginning of the chapter. Adrenaline and epinephrine are two names for the same molecule. The adrenal gland (in Latin, ad- = “on top of”; renal = “kidney”) secretes adrenaline. The ending “-ine” refers to the chemical being derived, or extracted, from the adrenal gland. A similar construction from Greek instead of Latin results in the word epinephrine (epi- = “above”; nephr- = “kidney”). In scientific usage, epinephrine is preferred in the United States, whereas adrenaline is preferred in Great Britain, because “adrenalin” was once a registered, proprietary drug name in the United States. Though the drug is no longer sold, the convention of referring to this molecule by the two different names persists. Similarly, norepinephrine and noradrenaline are two names for the same molecule.

Having understood the cholinergic and adrenergic systems, their role in the autonomic system is relatively simple to understand. All preganglionic fibers, both sympathetic and parasympathetic, release ACh. All ganglionic neurons—the targets of these preganglionic fibers—have nicotinic receptors in their cell membranes. The nicotinic receptor is a ligand-gated cation channel that results in depolarization of the postsynaptic membrane. The postganglionic parasympathetic fibers also release ACh, but the receptors on their targets are muscarinic receptors, which are G protein-coupled receptors and do not exclusively cause depolarization of the postsynaptic membrane. Postganglionic sympathetic fibers release norepinephrine, except for fibers that project to sweat glands and to blood vessels associated with skeletal muscles, which release ACh ([Table 15.1](#)).

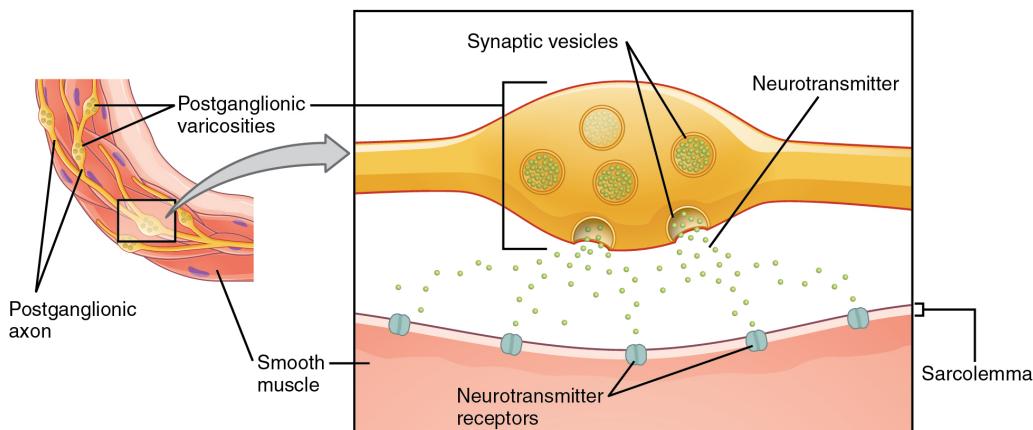
## Autonomic System Signaling Molecules

	Sympathetic	Parasympathetic
Preganglionic	Acetylcholine → nicotinic receptor	Acetylcholine → nicotinic receptor
Postganglionic	Norepinephrine → α- or β-adrenergic receptors Acetylcholine → muscarinic receptor (associated with sweat glands and the blood vessels associated with skeletal muscles only)	Acetylcholine → muscarinic receptor

**TABLE 15.1**

Signaling molecules can belong to two broad groups. Neurotransmitters are released at synapses, whereas hormones are released into the bloodstream. These are simplistic definitions, but they can help to clarify this point. Acetylcholine can be considered a neurotransmitter because it is released by axons at synapses. The adrenergic system, however, presents a challenge. Postganglionic sympathetic fibers release norepinephrine, which can be considered a neurotransmitter. But the adrenal medulla releases epinephrine and norepinephrine into circulation, so they should be considered hormones.

What are referred to here as synapses may not fit the strictest definition of synapse. Some sources will refer to the connection between a postganglionic fiber and a target effector as neuroeffector junctions; neurotransmitters, as defined above, would be called neuromodulators. The structure of postganglionic connections are not the typical synaptic end bulb that is found at the neuromuscular junction, but rather are chains of swellings along the length of a postganglionic fiber called a **varicosity** (Figure 15.5).



**FIGURE 15.5 Autonomic Varicosities** The connection between autonomic fibers and target effectors is not the same as the typical synapse, such as the neuromuscular junction. Instead of a synaptic end bulb, a neurotransmitter is released from swellings along the length of a fiber that makes an extended network of connections in the target effector.

### Everyday Connection

#### Fight or Flight? What About Fight and Freeze?

The original usage of the epithet “fight or flight” comes from a scientist named Walter Cannon who worked at Harvard in 1915. The concept of homeostasis and the functioning of the sympathetic system had been introduced in France in the previous century. Cannon expanded the idea, and introduced the idea that an animal responds to a threat by preparing to stand and fight or run away. The nature of this response was thoroughly explained in a book on the physiology of pain, hunger, fear, and rage.

When students learn about the sympathetic system and the fight-or-flight response, they often stop and wonder about other responses. If you were faced with a lioness running toward you as pictured at the beginning of this

chapter, would you run or would you stand your ground? Some people would say that they would freeze and not know what to do. So isn't there really more to what the autonomic system does than fight, flight, rest, or digest. What about fear and paralysis in the face of a threat?

The common epithet of "fight or flight" is being enlarged to be "fight, flight, or fright" or even "fight, flight, fright, or freeze." Cannon's original contribution was a catchy phrase to express some of what the nervous system does in response to a threat, but it is incomplete. The sympathetic system is responsible for the physiological responses to emotional states. The name "sympathetic" can be said to mean that (sym- = "together"; -pathos = "pain," "suffering," or "emotion").

### **INTERACTIVE LINK**

Watch this [video](http://openstax.org/l/nervsystem1) (<http://openstax.org/l/nervsystem1>) to learn more about the nervous system. As described in this video, the nervous system has a way to deal with threats and stress that is separate from the conscious control of the somatic nervous system. The system comes from a time when threats were about survival, but in the modern age, these responses become part of stress and anxiety. This video describes how the autonomic system is only part of the response to threats, or stressors. What other organ system gets involved, and what part of the brain coordinates the two systems for the entire response, including epinephrine (adrenaline) and cortisol?

## 15.2 Autonomic Reflexes and Homeostasis

### LEARNING OBJECTIVES

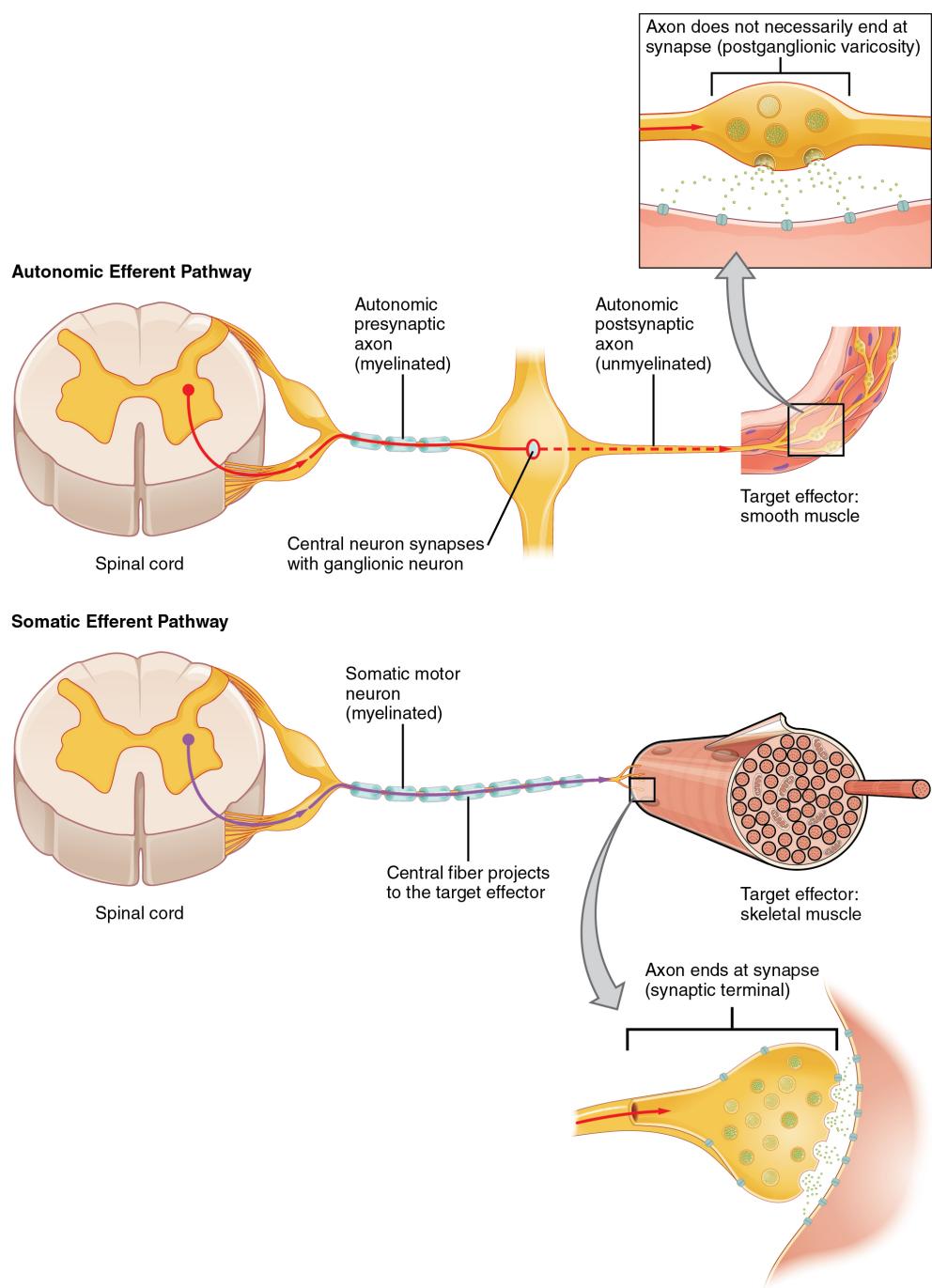
By the end of this section, you will be able to:

- Compare the structure of somatic and autonomic reflex arcs
- Explain the differences in sympathetic and parasympathetic reflexes
- Differentiate between short and long reflexes
- Determine the effect of the autonomic nervous system on the regulation of the various organ systems on the basis of the signaling molecules involved
- Describe the effects of drugs that affect autonomic function

The autonomic nervous system regulates organ systems through circuits that resemble the reflexes described in the somatic nervous system. The main difference between the somatic and autonomic systems is in what target tissues are effectors. Somatic responses are solely based on skeletal muscle contraction. The autonomic system, however, targets cardiac and smooth muscle, as well as glandular tissue. Whereas the basic circuit is a **reflex arc**, there are differences in the structure of those reflexes for the somatic and autonomic systems.

### The Structure of Reflexes

One difference between a **somatic reflex**, such as the withdrawal reflex, and a **visceral reflex**, which is an autonomic reflex, is in the **efferent branch**. The output of a somatic reflex is the lower motor neuron in the ventral horn of the spinal cord that projects directly to a skeletal muscle to cause its contraction. The output of a visceral reflex is a two-step pathway starting with the preganglionic fiber emerging from a lateral horn neuron in the spinal cord, or a cranial nucleus neuron in the brain stem, to a ganglion—followed by the postganglionic fiber projecting to a target effector. The other part of a reflex, the **afferent branch**, is often the same between the two systems. Sensory neurons receiving input from the periphery—with cell bodies in the sensory ganglia, either of a cranial nerve or a dorsal root ganglion adjacent to the spinal cord—project into the CNS to initiate the reflex (Figure 15.6). The Latin root “effere” means “to carry.” Adding the prefix “ef-” suggests the meaning “to carry away,” whereas adding the prefix “af-” suggests “to carry toward or inward.”



**FIGURE 15.6 Comparison of Somatic and Visceral Reflexes** The afferent inputs to somatic and visceral reflexes are essentially the same, whereas the efferent branches are different. Somatic reflexes, for instance, involve a direct connection from the ventral horn of the spinal cord to the skeletal muscle. Visceral reflexes involve a projection from the central neuron to a ganglion, followed by a second projection from the ganglion to the target effector.

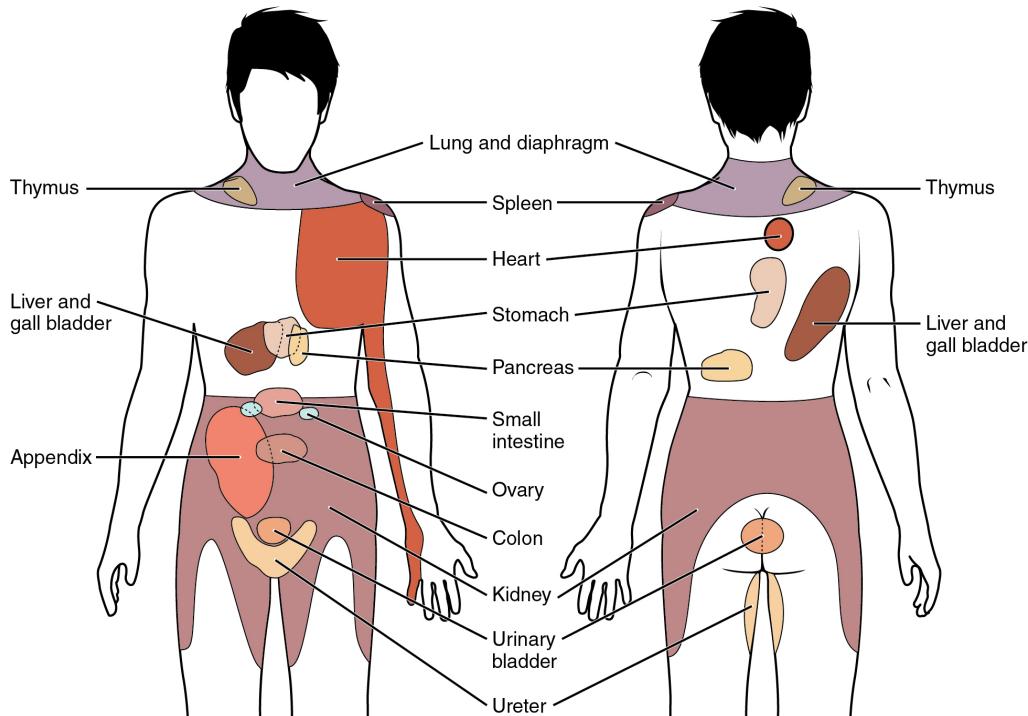
### Afferent Branch

The afferent branch of a reflex arc does differ between somatic and visceral reflexes in some instances. Many of the inputs to visceral reflexes are from special or somatic senses, but particular senses are associated with the viscera that are not part of the conscious perception of the environment through the somatic nervous system. For example, there is a specific type of mechanoreceptor, called a **baroreceptor**, in the walls of the aorta and carotid sinuses that senses the stretch of those organs when blood volume or pressure increases. You do not have a conscious perception of having high blood pressure, but that is an important afferent branch of the cardiovascular and, particularly, vasomotor reflexes. The sensory neuron is essentially the same as any other general sensory neuron. The baroreceptor apparatus is part of the ending of a unipolar neuron that has a cell body in a sensory ganglion. The

baroreceptors from the carotid arteries have axons in the glossopharyngeal nerve, and those from the aorta have axons in the vagus nerve.

Though visceral sensations are not primarily a part of conscious perception, those sensations sometimes make it to conscious awareness. If a visceral sense is strong enough, it will be perceived. The sensory homunculus—the representation of the body in the primary somatosensory cortex—only has a small region allotted for the perception of internal stimuli. If you swallow a large bolus of food, for instance, you will probably feel the lump of that food as it pushes through your esophagus, or even if your stomach is distended after a large meal. If you inhale especially cold air, you can feel it as it enters your larynx and trachea. These sensations are not the same as feeling high blood pressure or blood sugar levels.

When particularly strong visceral sensations rise to the level of conscious perception, the sensations are often felt in unexpected places. For example, strong visceral sensations of the heart will be felt as pain in the left shoulder and left arm. This irregular pattern of projection of conscious perception of visceral sensations is called **referred pain**. Depending on the organ system affected, the referred pain will project to different areas of the body (Figure 15.7). The location of referred pain is not random, but a definitive explanation of the mechanism has not been established. The most broadly accepted theory for this phenomenon is that the visceral sensory fibers enter into the same level of the spinal cord as the somatosensory fibers of the referred pain location. By this explanation, the visceral sensory fibers from the mediastinal region, where the heart is located, would enter the spinal cord at the same level as the spinal nerves from the shoulder and arm, so the brain misinterprets the sensations from the mediastinal region as being from the axillary and brachial regions. Projections from the medial and inferior divisions of the cervical ganglia do enter the spinal cord at the middle to lower cervical levels, which is where the somatosensory fibers enter.



**FIGURE 15.7** **Referred Pain Chart** Conscious perception of visceral sensations map to specific regions of the body, as shown in this chart. Some sensations are felt locally, whereas others are perceived as affecting areas that are quite distant from the involved organ.

### Disorders of the...

#### Nervous System: Kehr's Sign

Kehr's sign is the presentation of pain in the left shoulder, chest, and neck regions following rupture of the spleen. The spleen is in the upper-left abdominopelvic quadrant, but the pain is more in the shoulder and neck. How can this be? The sympathetic fibers connected to the spleen are from the celiac ganglion, which would be

from the mid-thoracic to lower thoracic region whereas parasympathetic fibers are found in the vagus nerve, which connects in the medulla of the brain stem. However, the neck and shoulder would connect to the spinal cord at the mid-cervical level of the spinal cord. These connections do not fit with the expected correspondence of visceral and somatosensory fibers entering at the same level of the spinal cord.

The incorrect assumption would be that the visceral sensations are coming from the spleen directly. In fact, the visceral fibers are coming from the diaphragm. The nerve connecting to the diaphragm takes a special route. The phrenic nerve is connected to the spinal cord at cervical levels 3 to 5. The motor fibers that make up this nerve are responsible for the muscle contractions that drive ventilation. These fibers have left the spinal cord to enter the phrenic nerve, meaning that spinal cord damage below the mid-cervical level is not fatal by making ventilation impossible. Therefore, the visceral fibers from the diaphragm enter the spinal cord at the same level as the somatosensory fibers from the neck and shoulder.

The diaphragm plays a role in Kehr's sign because the spleen is just inferior to the diaphragm in the upper-left quadrant of the abdominopelvic cavity. When the spleen ruptures, blood spills into this region. The accumulating hemorrhage then puts pressure on the diaphragm. The visceral sensation is actually in the diaphragm, so the referred pain is in a region of the body that corresponds to the diaphragm, not the spleen.

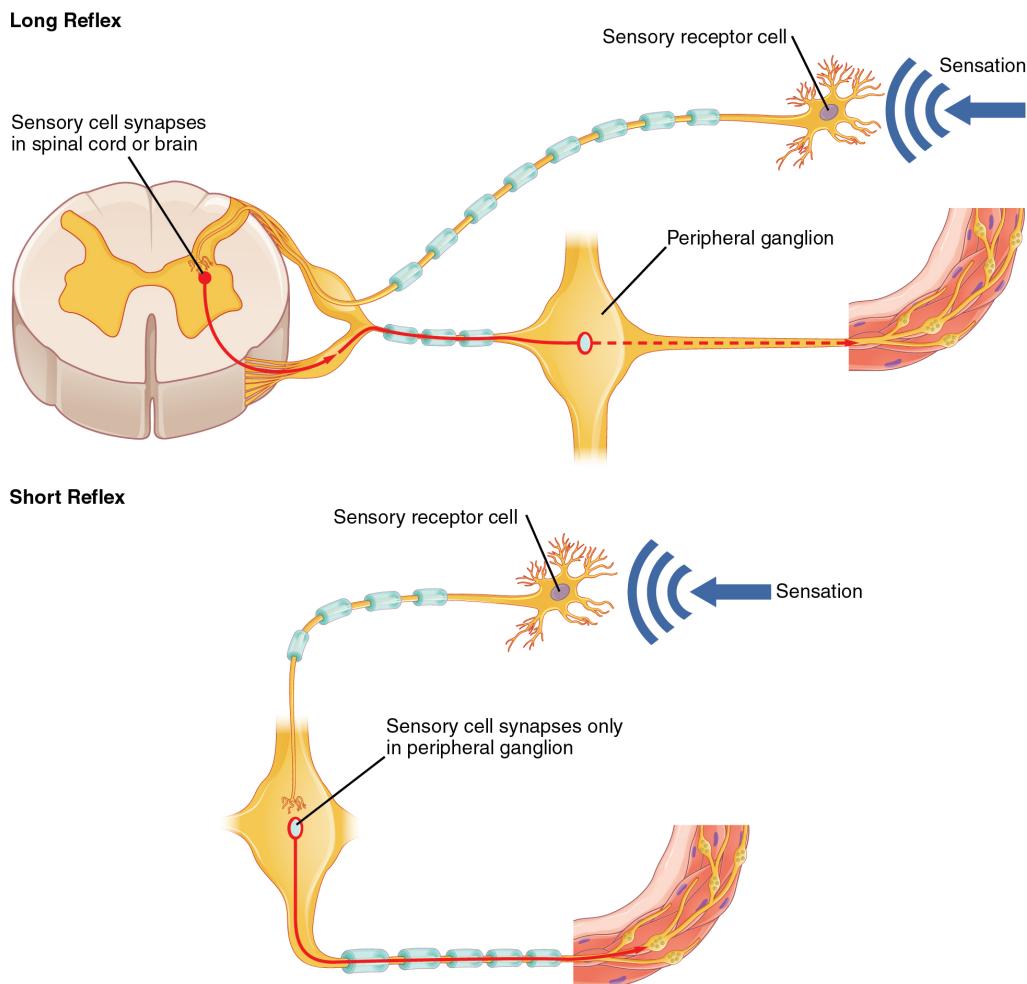
### Efferent Branch

The efferent branch of the visceral reflex arc begins with the projection from the central neuron along the preganglionic fiber. This fiber then makes a synapse on the ganglionic neuron that projects to the target effector.

The effector organs that are the targets of the autonomic system range from the iris and ciliary body of the eye to the urinary bladder and reproductive organs. The thoracolumbar output, through the various sympathetic ganglia, reaches all of these organs. The cranial component of the parasympathetic system projects from the eye to part of the intestines. The sacral component picks up with the majority of the large intestine and the pelvic organs of the urinary and reproductive systems.

### Short and Long Reflexes

Somatic reflexes involve sensory neurons that connect sensory receptors to the CNS and motor neurons that project back out to the skeletal muscles. Visceral reflexes that involve the thoracolumbar or craniosacral systems share similar connections. However, there are reflexes that do not need to involve any CNS components. A **long reflex** has afferent branches that enter the spinal cord or brain and involve the efferent branches, as previously explained. A **short reflex** is completely peripheral and only involves the local integration of sensory input with motor output ([Figure 15.8](#)).



**FIGURE 15.8 Short and Long Reflexes** Sensory input can stimulate either a short or a long reflex. A sensory neuron can project to the CNS or to an autonomic ganglion. The short reflex involves the direct stimulation of a postganglionic fiber by the sensory neuron, whereas the long reflex involves integration in the spinal cord or brain.

The difference between short and long reflexes is in the involvement of the CNS. Somatic reflexes always involve the CNS, even in a monosynaptic reflex in which the sensory neuron directly activates the motor neuron. That synapse is in the spinal cord or brain stem, so it has to involve the CNS. However, in the autonomic system there is the possibility that the CNS is not involved. Because the efferent branch of a visceral reflex involves two neurons—the central neuron and the ganglionic neuron—a “short circuit” can be possible. If a sensory neuron projects directly to the ganglionic neuron and causes it to activate the effector target, then the CNS is not involved.

A division of the nervous system that is related to the autonomic nervous system is the enteric nervous system. The word enteric refers to the digestive organs, so this represents the nervous tissue that is part of the digestive system. There are a few myenteric plexuses in which the nervous tissue in the wall of the digestive tract organs can directly influence digestive function. If stretch receptors in the stomach are activated by the filling and distension of the stomach, a short reflex will directly activate the smooth muscle fibers of the stomach wall to increase motility to digest the excessive food in the stomach. No CNS involvement is needed because the stretch receptor is directly activating a neuron in the wall of the stomach that causes the smooth muscle to contract. That neuron, connected to the smooth muscle, is a postganglionic parasympathetic neuron that can be controlled by a fiber found in the vagus nerve.

### INTERACTIVE LINK

Read this [article](http://openstax.org/l/strokespell) (<http://openstax.org/l/strokespell>) to learn about a teenager who experiences a series of spells that suggest a stroke. He undergoes endless tests and seeks input from multiple doctors. In the end, one expert, one

question, and a simple blood pressure cuff answers the question. Why would the heart have to beat faster when the teenager changes his body position from lying down to sitting, and then to standing?

## Balance in Competing Autonomic Reflex Arcs

The autonomic nervous system is important for homeostasis because its two divisions compete at the target effector. The balance of homeostasis is attributable to the competing inputs from the sympathetic and parasympathetic divisions (dual innervation). At the level of the target effector, the signal of which system is sending the message is strictly chemical. A signaling molecule binds to a receptor that causes changes in the target cell, which in turn causes the tissue or organ to respond to the changing conditions of the body.

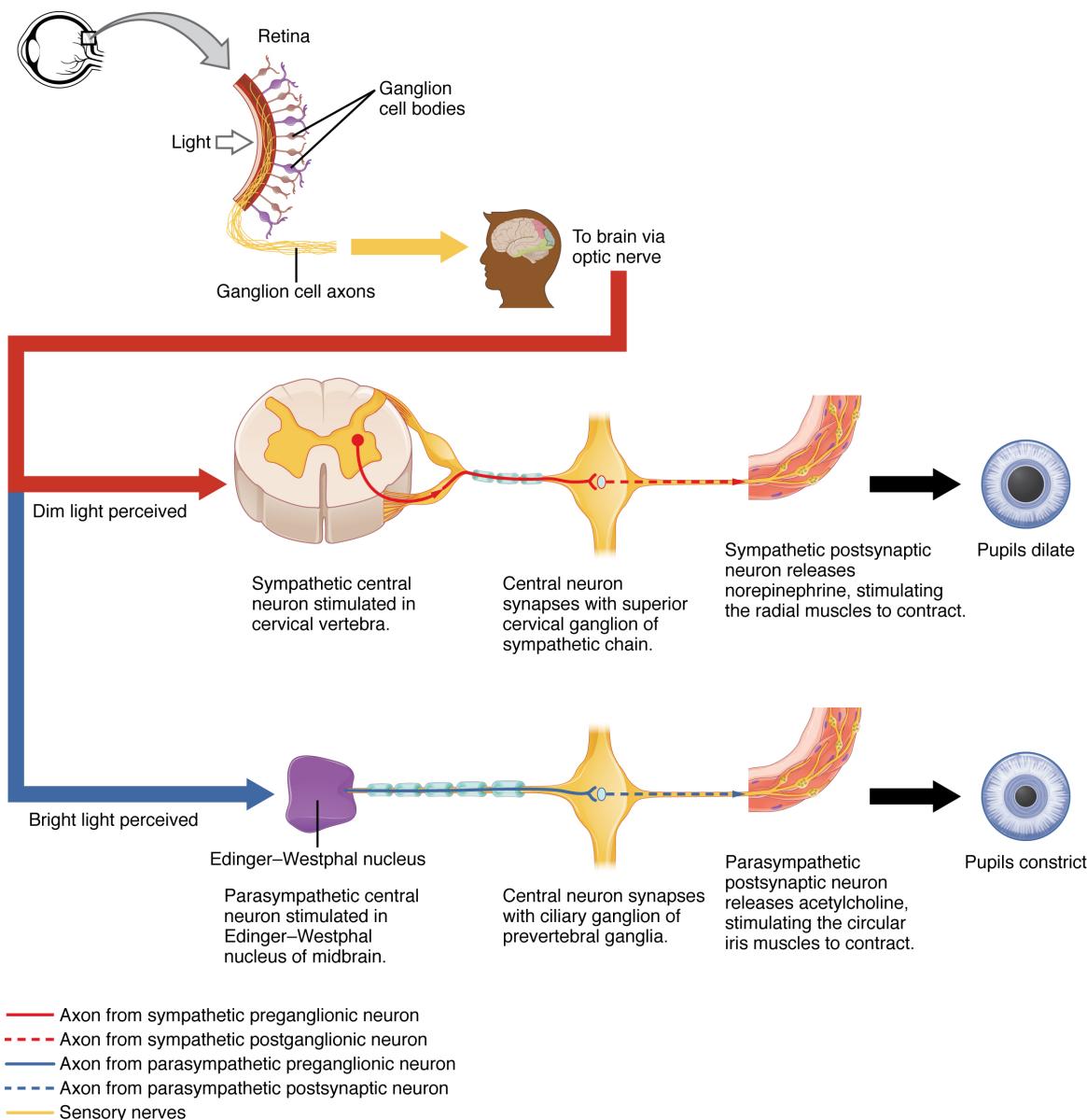
### Competing Neurotransmitters

The postganglionic fibers of the sympathetic and parasympathetic divisions both release neurotransmitters that bind to receptors on their targets. Postganglionic sympathetic fibers release norepinephrine, with a minor exception, whereas postganglionic parasympathetic fibers release ACh. For any given target, the difference in which division of the autonomic nervous system is exerting control is just in what chemical binds to its receptors. The target cells will have adrenergic and muscarinic receptors. If norepinephrine is released, it will bind to the adrenergic receptors present on the target cell, and if ACh is released, it will bind to the muscarinic receptors on the target cell.

In the sympathetic system, there are exceptions to this pattern of dual innervation. The postganglionic sympathetic fibers that contact the blood vessels within skeletal muscle and that contact sweat glands do not release norepinephrine, they release ACh. This does not create any problem because there is no parasympathetic input to the sweat glands. Sweat glands have muscarinic receptors and produce and secrete sweat in response to the presence of ACh.

At most of the other targets of the autonomic system, the effector response is based on which neurotransmitter is released and what receptor is present. For example, regions of the heart that establish heart rate are contacted by postganglionic fibers from both systems. If norepinephrine is released onto those cells, it binds to an adrenergic receptor that causes the cells to depolarize faster, and the heart rate increases. If ACh is released onto those cells, it binds to a muscarinic receptor that causes the cells to hyperpolarize so that they cannot reach threshold as easily, and the heart rate slows. Without this parasympathetic input, the heart would work at a rate of approximately 100 beats per minute (bpm). The sympathetic system speeds that up, as it would during exercise, to 120–140 bpm, for example. The parasympathetic system slows it down to the resting heart rate of 60–80 bpm.

Another example is in the control of pupillary size ([Figure 15.9](#)). The afferent branch responds to light hitting the retina. Photoreceptors are activated, and the signal is transferred to the retinal ganglion cells that send an action potential along the optic nerve into the diencephalon. If light levels are low, the sympathetic system sends a signal out through the upper thoracic spinal cord to the superior cervical ganglion of the sympathetic chain. The postganglionic fiber then projects to the iris, where it releases norepinephrine onto the radial fibers of the iris (a smooth muscle). When those fibers contract, the pupil dilates—increasing the amount of light hitting the retina. If light levels are too high, the parasympathetic system sends a signal out from the Edinger-Westphal nucleus through the oculomotor nerve. This fiber synapses in the ciliary ganglion in the posterior orbit. The postganglionic fiber then projects to the iris, where it releases ACh onto the circular fibers of the iris—another smooth muscle. When those fibers contract, the pupil constricts to limit the amount of light hitting the retina.



**FIGURE 15.9 Autonomic Control of Pupillary Size** Activation of the pupillary reflex comes from the amount of light activating the retinal ganglion cells, as sent along the optic nerve. The output of the sympathetic system projects through the superior cervical ganglion, whereas the parasympathetic system originates out of the midbrain and projects through the oculomotor nerve to the ciliary ganglion, which then projects to the iris. The postganglionic fibers of either division release neurotransmitters onto the smooth muscles of the iris to cause changes in the pupillary size. Norepinephrine results in dilation and ACh results in constriction.

In this example, the autonomic system is controlling how much light hits the retina. It is a homeostatic reflex mechanism that keeps the activation of photoreceptors within certain limits. In the context of avoiding a threat like the lioness on the savannah, the sympathetic response for fight or flight will increase pupillary diameter so that more light hits the retina and more visual information is available for running away. Likewise, the parasympathetic response of rest reduces the amount of light reaching the retina, allowing the photoreceptors to cycle through bleaching and be regenerated for further visual perception; this is what the homeostatic process is attempting to maintain.

### INTERACTIVE LINK

Watch this [video \(<http://openstax.org/l/pupillary>\)](http://openstax.org/l/pupillary) to learn about the pupillary reflexes. The pupillary light reflex involves sensory input through the optic nerve and motor response through the oculomotor nerve to the ciliary ganglion, which projects to the circular fibers of the iris. As shown in this short animation, pupils will constrict to limit the amount of light falling on the retina under bright lighting conditions. What constitutes the afferent and

efferent branches of the competing reflex (dilation)?

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### Autonomic Tone

Organ systems are balanced between the input from the sympathetic and parasympathetic divisions. When something upsets that balance, the homeostatic mechanisms strive to return it to its regular state. For each organ system, there may be more of a sympathetic or parasympathetic tendency to the resting state, which is known as the **autonomic tone** of the system. For example, the heart rate was described above. Because the resting heart rate is the result of the parasympathetic system slowing the heart down from its intrinsic rate of 100 bpm, the heart can be said to be in parasympathetic tone.

In a similar fashion, another aspect of the cardiovascular system is primarily under sympathetic control. Blood pressure is partially determined by the contraction of smooth muscle in the walls of blood vessels. These tissues have adrenergic receptors that respond to the release of norepinephrine from postganglionic sympathetic fibers by constricting and increasing blood pressure. The hormones released from the adrenal medulla—epinephrine and norepinephrine—will also bind to these receptors. Those hormones travel through the bloodstream where they can easily interact with the receptors in the vessel walls. The parasympathetic system has no significant input to the systemic blood vessels, so the sympathetic system determines their tone.

There are a limited number of blood vessels that respond to sympathetic input in a different fashion. Blood vessels in skeletal muscle, particularly those in the lower limbs, are more likely to dilate. It does not have an overall effect on blood pressure to alter the tone of the vessels, but rather allows for blood flow to increase for those skeletal muscles that will be active in the fight-or-flight response. The blood vessels that have a parasympathetic projection are limited to those in the erectile tissue of the reproductive organs. Acetylcholine released by these postganglionic parasympathetic fibers cause the vessels to dilate, leading to the engorgement of the erectile tissue.



## HOMEOSTATIC IMBALANCES

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### Orthostatic Hypotension

Have you ever stood up quickly and felt dizzy for a moment? This is because, for one reason or another, blood is not getting to your brain so it is briefly deprived of oxygen. When you change position from sitting or lying down to standing, your cardiovascular system has to adjust for a new challenge, keeping blood pumping up into the head while gravity is pulling more and more blood down into the legs.

The reason for this is a sympathetic reflex that maintains the output of the heart in response to postural change. When a person stands up, proprioceptors indicate that the body is changing position. A signal goes to the CNS, which then sends a signal to the upper thoracic spinal cord neurons of the sympathetic division. The sympathetic system then causes the heart to beat faster and the blood vessels to constrict. Both changes will make it possible for the cardiovascular system to maintain the rate of blood delivery to the brain. Blood is being pumped superiorly through the internal branch of the carotid arteries into the brain, against the force of gravity. Gravity is not increasing while standing, but blood is more likely to flow down into the legs as they are extended for standing. This sympathetic reflex keeps the brain well oxygenated so that cognitive and other neural processes are not interrupted.

Sometimes this does not work properly. If the sympathetic system cannot increase cardiac output, then blood pressure into the brain will decrease, and a brief neurological loss can be felt. This can be brief, as a slight “wooziness” when standing up too quickly, or a loss of balance and neurological impairment for a period of time. The name for this is orthostatic hypotension, which means that blood pressure goes below the homeostatic set point when standing. It can be the result of standing up faster than the reflex can occur, which may be referred to as a benign “head rush,” or it may be the result of an underlying cause.

There are two basic reasons that orthostatic hypotension can occur. First, blood volume is too low and the sympathetic reflex is not effective. This hypovolemia may be the result of dehydration or medications that affect fluid balance, such as diuretics or vasodilators. Both of these medications are meant to lower blood pressure, which may be necessary in the case of systemic hypertension, and regulation of the medications may alleviate the problem. Sometimes increasing fluid intake or water retention through salt intake can improve the situation.

The second underlying cause of orthostatic hypotension is autonomic failure. There are several disorders that result in compromised sympathetic functions. The disorders range from diabetes to multiple system atrophy (a loss of control over many systems in the body), and addressing the underlying condition can improve the hypotension. For example, with diabetes, peripheral nerve damage can occur, which would affect the postganglionic sympathetic fibers. Getting blood glucose levels under control can improve neurological deficits associated with diabetes.

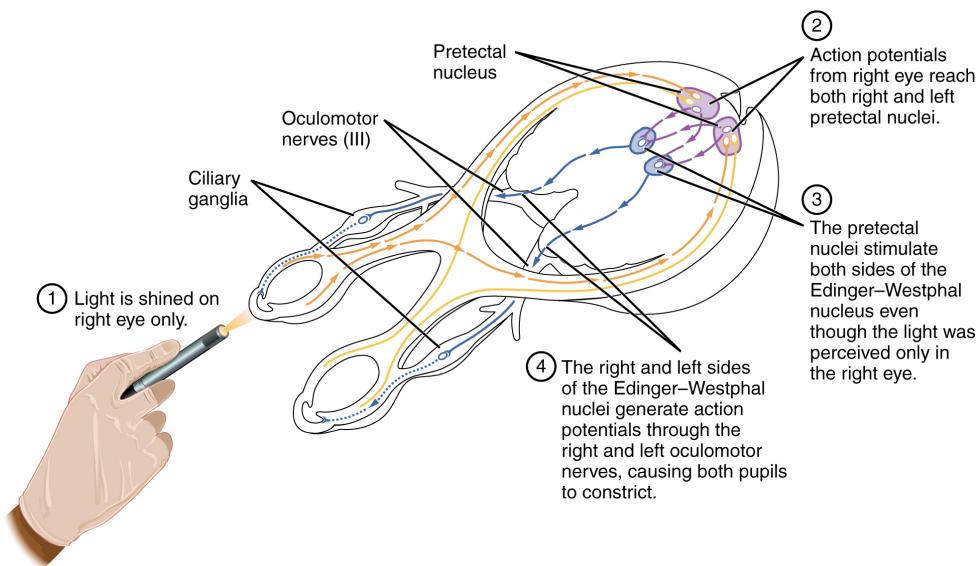
## 15.3 Central Control

### LEARNING OBJECTIVES

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

- Describe the role of higher centers of the brain in autonomic regulation
- Explain the connection of the hypothalamus to homeostasis
- Describe the regions of the CNS that link the autonomic system with emotion
- Describe the pathways important to descending control of the autonomic system

The pupillary light reflex (Figure 15.10) begins when light hits the retina and causes a signal to travel along the optic nerve. This is visual sensation, because the afferent branch of this reflex is simply sharing the special sense pathway. Bright light hitting the retina leads to the parasympathetic response, through the oculomotor nerve, followed by the postganglionic fiber from the ciliary ganglion, which stimulates the circular fibers of the iris to contract and constrict the pupil. When light hits the retina in one eye, both pupils contract. When that light is removed, both pupils dilate again back to the resting position. When the stimulus is unilateral (presented to only one eye), the response is bilateral (both eyes). The same is not true for somatic reflexes. If you touch a hot radiator, you only pull that arm back, not both. Central control of autonomic reflexes is different than for somatic reflexes. The hypothalamus, along with other CNS locations, controls the autonomic system.



**FIGURE 15.10 Pupillary Reflex Pathways** The pupil is under competing autonomic control in response to light levels hitting the retina. The sympathetic system will dilate the pupil when the retina is not receiving enough light, and the parasympathetic system will constrict the pupil when too much light hits the retina.

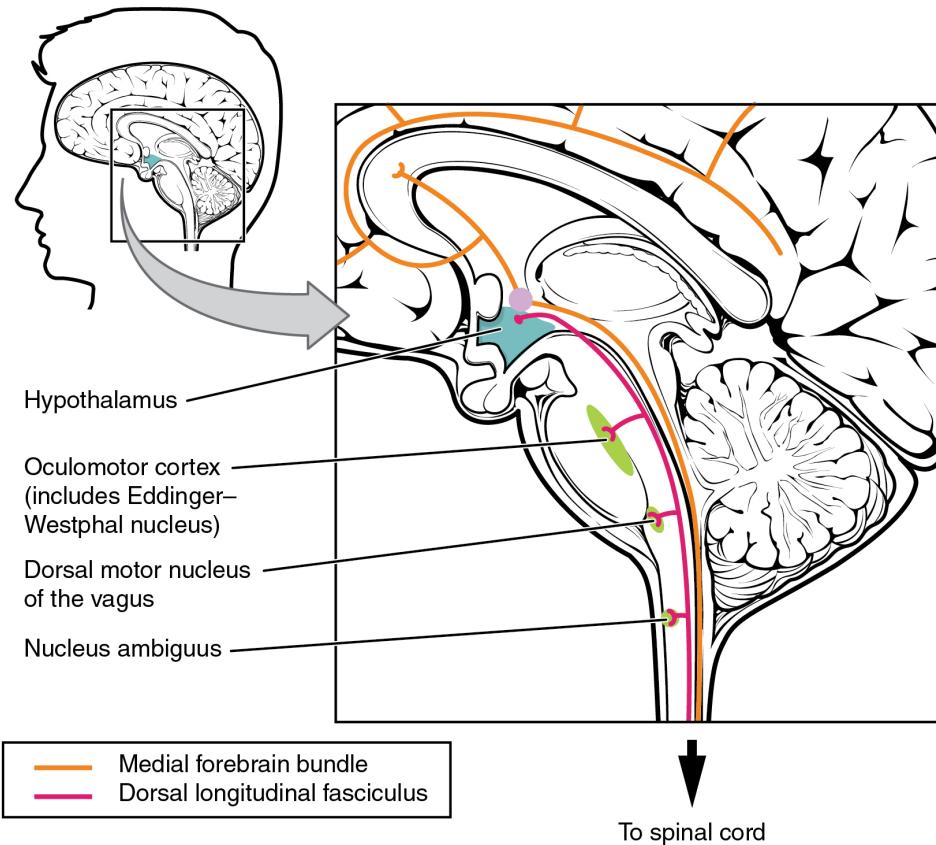
### Forebrain Structures

Autonomic control is based on the visceral reflexes, composed of the afferent and efferent branches. These homeostatic mechanisms are based on the balance between the two divisions of the autonomic system, which results in tone for various organs that is based on the predominant input from the sympathetic or parasympathetic systems. Coordinating that balance requires integration that begins with forebrain structures like the hypothalamus and continues into the brain stem and spinal cord.

### The Hypothalamus

The hypothalamus is the control center for many homeostatic mechanisms. It regulates both autonomic function and endocrine function. The roles it plays in the pupillary reflexes demonstrates the importance of this control center. The optic nerve projects primarily to the thalamus, which is the necessary relay to the occipital cortex for conscious visual perception. Another projection of the optic nerve, however, goes to the hypothalamus.

The hypothalamus then uses this visual system input to drive the pupillary reflexes. If the retina is activated by high levels of light, the hypothalamus stimulates the parasympathetic response. If the optic nerve message shows that low levels of light are falling on the retina, the hypothalamus activates the sympathetic response. Output from the hypothalamus follows two main tracts, the **dorsal longitudinal fasciculus** and the **medial forebrain bundle** ([Figure 15.11](#)). Along these two tracts, the hypothalamus can influence the Edinger–Westphal nucleus of the oculomotor complex or the lateral horns of the thoracic spinal cord.



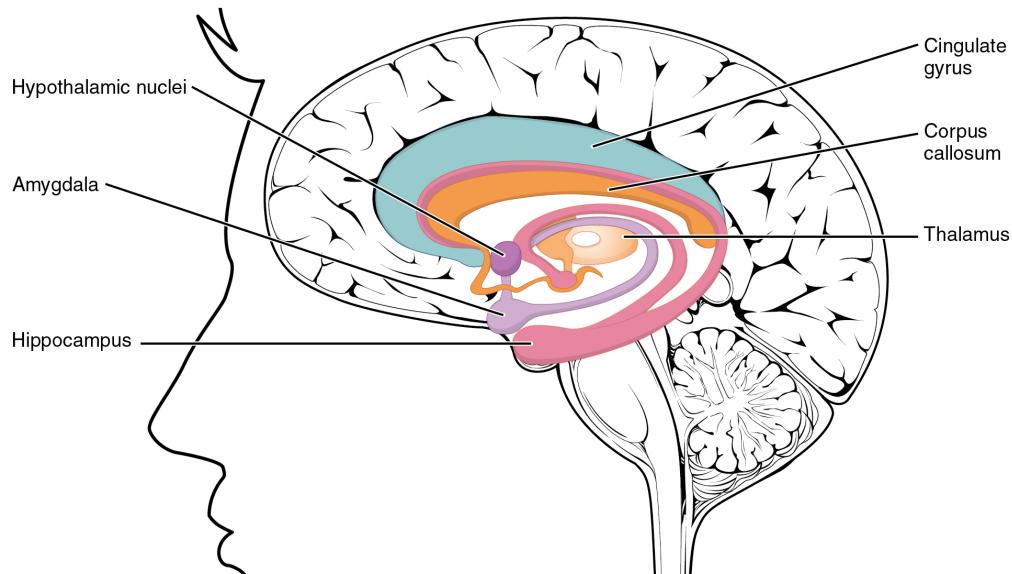
**FIGURE 15.11 Fiber Tracts of the Central Autonomic System** The hypothalamus is the source of most of the central control of autonomic function. It receives input from cerebral structures and projects to brain stem and spinal cord structures to regulate the balance of sympathetic and parasympathetic input to the organ systems of the body. The main pathways for this are the medial forebrain bundle and the dorsal longitudinal fasciculus.

These two tracts connect the hypothalamus with the major parasympathetic nuclei in the brain stem and the preganglionic (central) neurons of the thoracolumbar spinal cord. The hypothalamus also receives input from other areas of the forebrain through the medial forebrain bundle. The olfactory cortex, the septal nuclei of the basal forebrain, and the amygdala project into the hypothalamus through the medial forebrain bundle. These forebrain structures inform the hypothalamus about the state of the nervous system and can influence the regulatory processes of homeostasis. A good example of this is found in the amygdala, which is found beneath the cerebral cortex of the temporal lobe and plays a role in our ability to remember and feel emotions.

### The Amygdala

The amygdala is a group of nuclei in the medial region of the temporal lobe that is part of the **limbic lobe** ([Figure 15.12](#)). The limbic lobe includes structures that are involved in emotional responses, as well as structures that contribute to memory function. The limbic lobe has strong connections with the hypothalamus and influences the

state of its activity on the basis of emotional state. For example, when you are anxious or scared, the amygdala will send signals to the hypothalamus along the medial forebrain bundle that will stimulate the sympathetic fight-or-flight response. The hypothalamus will also stimulate the release of stress hormones through its control of the endocrine system in response to amygdala input.



**FIGURE 15.12 The Limbic Lobe** Structures arranged around the edge of the cerebrum constitute the limbic lobe, which includes the amygdala, hippocampus, and cingulate gyrus, and connects to the hypothalamus.

### The Medulla

The medulla contains nuclei referred to as the **cardiovascular center**, which controls the smooth and cardiac muscle of the cardiovascular system through autonomic connections. When the homeostasis of the cardiovascular system shifts, such as when blood pressure changes, the coordination of the autonomic system can be accomplished within this region. Furthermore, when descending inputs from the hypothalamus stimulate this area, the sympathetic system can increase activity in the cardiovascular system, such as in response to anxiety or stress. The preganglionic sympathetic fibers that are responsible for increasing heart rate are referred to as the **cardiac accelerator nerves**, whereas the preganglionic sympathetic fibers responsible for constricting blood vessels compose the **vasomotor nerves**.

Several brain stem nuclei are important for the visceral control of major organ systems. One brain stem nucleus involved in cardiovascular function is the solitary nucleus. It receives sensory input about blood pressure and cardiac function from the glossopharyngeal and vagus nerves, and its output will activate sympathetic stimulation of the heart or blood vessels through the upper thoracic lateral horn. Another brain stem nucleus important for visceral control is the dorsal motor nucleus of the vagus nerve, which is the motor nucleus for the parasympathetic functions ascribed to the vagus nerve, including decreasing the heart rate, relaxing bronchial tubes in the lungs, and activating digestive function through the enteric nervous system. The nucleus ambiguus, which is named for its ambiguous histology, also contributes to the parasympathetic output of the vagus nerve and targets muscles in the pharynx and larynx for swallowing and speech, as well as contributing to the parasympathetic tone of the heart along with the dorsal motor nucleus of the vagus.

### Everyday Connection

#### Exercise and the Autonomic System

In addition to its association with the fight-or-flight response and rest-and-digest functions, the autonomic system is responsible for certain everyday functions. For example, it comes into play when homeostatic mechanisms dynamically change, such as the physiological changes that accompany exercise. Getting on the treadmill and putting in a good workout will cause the heart rate to increase, breathing to be stronger and

deeper, sweat glands to activate, and the digestive system to suspend activity. These are the same physiological changes associated with the fight-or-flight response, but there is nothing chasing you on that treadmill.

This is not a simple homeostatic mechanism at work because “maintaining the internal environment” would mean getting all those changes back to their set points. Instead, the sympathetic system has become active during exercise so that your body can cope with what is happening. A homeostatic mechanism is dealing with the conscious decision to push the body away from a resting state. The heart, actually, is moving away from its homeostatic set point. Without any input from the autonomic system, the heart would beat at approximately 100 bpm, and the parasympathetic system slows that down to the resting rate of approximately 70 bpm. But in the middle of a good workout, you should see your heart rate at 120–140 bpm. You could say that the body is stressed because of what you are doing to it. Homeostatic mechanisms are trying to keep blood pH in the normal range, or to keep body temperature under control, but those are in response to the choice to exercise.

### INTERACTIVE LINK

Watch this [video](http://openstax.org/l/emotions) (<http://openstax.org/l/emotions>) to learn about physical responses to emotion. The autonomic system, which is important for regulating the homeostasis of the organ systems, is also responsible for our physiological responses to emotions such as fear. The video summarizes the extent of the body’s reactions and describes several effects of the autonomic system in response to fear. On the basis of what you have already studied about autonomic function, which effect would you expect to be associated with parasympathetic, rather than sympathetic, activity?

## 15.4 Drugs that Affect the Autonomic System

### LEARNING OBJECTIVES

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

- List the classes of pharmaceuticals that interact with the autonomic nervous system
- Differentiate between cholinergic and adrenergic compounds
- Differentiate between sympathomimetic and sympatholytic drugs
- Relate the consequences of nicotine abuse with respect to autonomic control of the cardiovascular system

An important way to understand the effects of native neurochemicals in the autonomic system is in considering the effects of pharmaceutical drugs. This can be considered in terms of how drugs change autonomic function. These effects will primarily be based on how drugs act at the receptors of the autonomic system neurochemistry. The signaling molecules of the nervous system interact with proteins in the cell membranes of various target cells. In fact, no effect can be attributed to just the signaling molecules themselves without considering the receptors. A chemical that the body produces to interact with those receptors is called an **endogenous chemical**, whereas a chemical introduced to the system from outside is an **exogenous chemical**. Exogenous chemicals may be of a natural origin, such as a plant extract, or they may be synthetically produced in a pharmaceutical laboratory.

### Broad Autonomic Effects

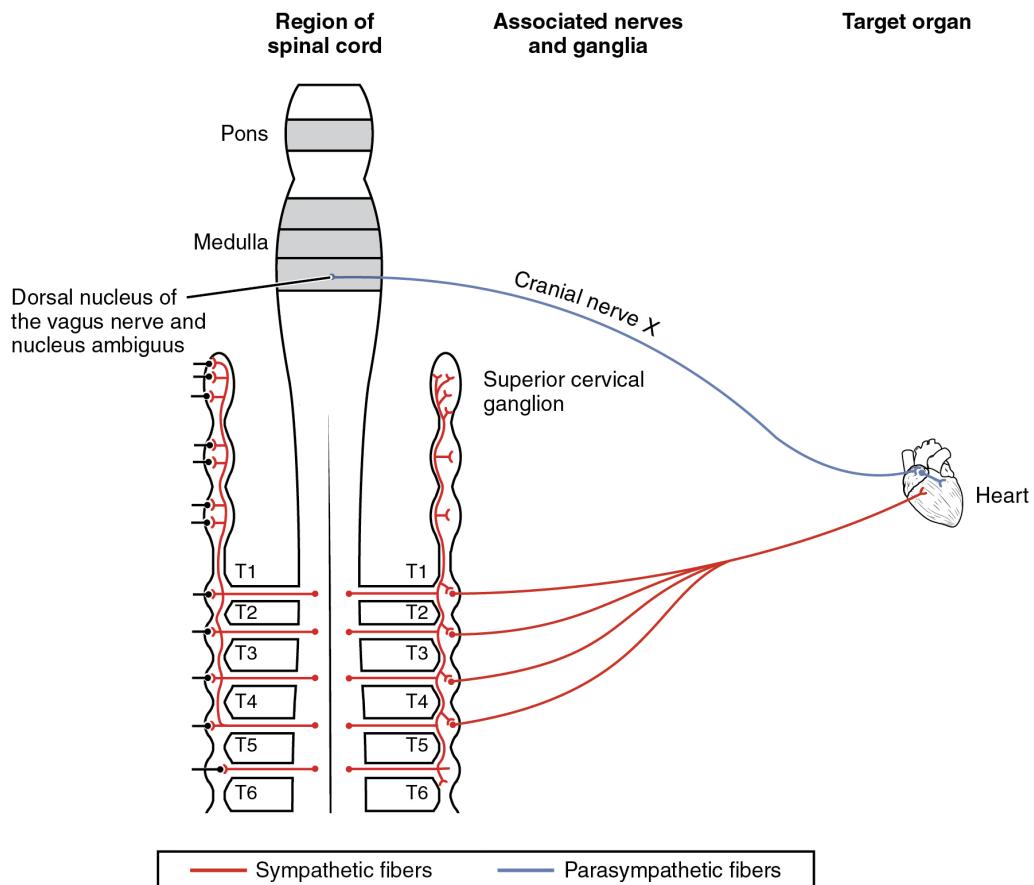
One important drug that affects the autonomic system broadly is not a pharmaceutical therapeutic agent associated with the system. This drug is nicotine. The effects of nicotine on the autonomic nervous system are important in considering the role smoking can play in health.

All ganglionic neurons of the autonomic system, in both sympathetic and parasympathetic ganglia, are activated by ACh released from preganglionic fibers. The ACh receptors on these neurons are of the nicotinic type, meaning that they are ligand-gated ion channels. When the neurotransmitter released from the preganglionic fiber binds to the receptor protein, a channel opens to allow positive ions to cross the cell membrane. The result is depolarization of the ganglia. Nicotine acts as an ACh analog at these synapses, so when someone takes in the drug, it binds to these ACh receptors and activates the ganglionic neurons, causing them to depolarize.

Ganglia of both divisions are activated equally by the drug. For many target organs in the body, this results in no net change. The competing inputs to the system cancel each other out and nothing significant happens. For example, the sympathetic system will cause sphincters in the digestive tract to contract, limiting digestive propulsion, but the

parasympathetic system will cause the contraction of other muscles in the digestive tract, which will try to push the contents of the digestive system along. The end result is that the food does not really move along and the digestive system has not appreciably changed.

The system in which this can be problematic is in the cardiovascular system, which is why smoking is a risk factor for cardiovascular disease. First, there is no significant parasympathetic regulation of blood pressure. Only a limited number of blood vessels are affected by parasympathetic input, so nicotine will preferentially cause the vascular tone to become more sympathetic, which means blood pressure will be increased. Second, the autonomic control of the heart is special. Unlike skeletal or smooth muscles, cardiac muscle is intrinsically active, meaning that it generates its own action potentials. The autonomic system does not cause the heart to beat, it just speeds it up (sympathetic) or slows it down (parasympathetic). The mechanisms for this are not mutually exclusive, so the heart receives conflicting signals, and the rhythm of the heart can be affected ([Figure 15.13](#)).



**FIGURE 15.13 Autonomic Connections to Heart and Blood Vessels** The nicotinic receptor is found on all autonomic ganglia, but the cardiovascular connections are particular, and do not conform to the usual competitive projections that would just cancel each other out when stimulated by nicotine. The opposing signals to the heart would both depolarize and hyperpolarize the heart cells that establish the rhythm of the heartbeat, likely causing arrhythmia. Only the sympathetic system governs systemic blood pressure so nicotine would cause an increase.

## Sympathetic Effect

The neurochemistry of the sympathetic system is based on the adrenergic system. Norepinephrine and epinephrine influence target effectors by binding to the  $\alpha$ -adrenergic or  $\beta$ -adrenergic receptors. Drugs that affect the sympathetic system affect these chemical systems. The drugs can be classified by whether they enhance the functions of the sympathetic system or interrupt those functions. A drug that enhances adrenergic function is known as a **sympathomimetic drug**, whereas a drug that interrupts adrenergic function is a **sympatholytic drug**.

### Sympathomimetic Drugs

When the sympathetic system is not functioning correctly or the body is in a state of homeostatic imbalance, these drugs act at postganglionic terminals and synapses in the sympathetic efferent pathway. These drugs either bind to

particular adrenergic receptors and mimic norepinephrine at the synapses between sympathetic postganglionic fibers and their targets, or they increase the production and release of norepinephrine from postganglionic fibers. Also, to increase the effectiveness of adrenergic chemicals released from the fibers, some of these drugs may block the removal or reuptake of the neurotransmitter from the synapse.

A common sympathomimetic drug is phenylephrine, which is a common component of decongestants. It can also be used to dilate the pupil and to raise blood pressure. Phenylephrine is known as an  $\alpha_1$ -adrenergic **agonist**, meaning that it binds to a specific adrenergic receptor, stimulating a response. In this role, phenylephrine will bind to the adrenergic receptors in bronchioles of the lungs and cause them to dilate. By opening these structures, accumulated mucus can be cleared out of the lower respiratory tract. Phenylephrine is often paired with other pharmaceuticals, such as analgesics, as in the “sinus” version of many over-the-counter drugs, such as Tylenol Sinus<sup>®</sup> or Excedrin Sinus<sup>®</sup>, or in expectorants for chest congestion such as in Robitussin CF<sup>®</sup>.

A related molecule, called pseudoephedrine, was much more commonly used in these applications than was phenylephrine, until the molecule became useful in the illicit production of amphetamines. Phenylephrine is not as effective as a drug because it can be partially broken down in the digestive tract before it is ever absorbed. Like the adrenergic agents, phenylephrine is effective in dilating the pupil, known as **mydriasis** (Figure 15.14).

Phenylephrine is used during an eye exam in an ophthalmologist’s or optometrist’s office for this purpose. It can also be used to increase blood pressure in situations in which cardiac function is compromised, such as under anesthesia or during septic shock.



**FIGURE 15.14 Mydriasis** The sympathetic system causes pupillary dilation when norepinephrine binds to an adrenergic receptor in the radial fibers of the iris smooth muscle. Phenylephrine mimics this action by binding to the same receptor when drops are applied onto the surface of the eye in a doctor’s office. (credit: Corey Theiss / Vulegenda/Wikimedia Commons)

Other drugs that enhance adrenergic function are not associated with therapeutic uses, but affect the functions of the sympathetic system in a similar fashion. Cocaine primarily interferes with the uptake of dopamine at the synapse and can also increase adrenergic function. Caffeine is an antagonist to a different neurotransmitter receptor, called the adenosine receptor. Adenosine will suppress adrenergic activity, specifically the release of norepinephrine at synapses, so caffeine indirectly increases adrenergic activity. There is some evidence that caffeine can aid in the therapeutic use of drugs, perhaps by potentiating (increasing) sympathetic function, as is suggested by the inclusion of caffeine in over-the-counter analgesics such as Excedrin<sup>®</sup>.

### Sympatholytic Drugs

Drugs that interfere with sympathetic function are referred to as sympatholytic, or sympathoplegic, drugs. They primarily work as an **antagonist** to the adrenergic receptors. They block the ability of norepinephrine or epinephrine to bind to the receptors so that the effect is “cut” or “takes a blow,” to refer to the endings “-lytic” and “-plegic,” respectively. The various drugs of this class will be specific to  $\alpha$ -adrenergic or  $\beta$ -adrenergic receptors, or to their receptor subtypes.

Possibly the most familiar type of sympatholytic drug are the  $\beta$ -blockers. These drugs are often used to treat cardiovascular disease because they block the  $\beta$ -receptors associated with vasoconstriction and cardioacceleration. By allowing blood vessels to dilate, or keeping heart rate from increasing, these drugs can improve cardiac function in a compromised system, such as for a person with congestive heart failure or who has previously suffered a heart attack. A couple of common versions of  $\beta$ -blockers are metoprolol, which specifically blocks the  $\beta_1$ -receptor, and propanolol, which nonspecifically blocks  $\beta$ -receptors. There are other drugs that are  $\alpha$ -blockers and can affect the sympathetic system in a similar way.

Other uses for sympatholytic drugs are as antianxiety medications. A common example of this is clonidine, which is an  $\alpha$ -agonist. The sympathetic system is tied to anxiety to the point that the sympathetic response can be referred

to as “fight, flight, or fright.” Clonidine is used for other treatments aside from hypertension and anxiety, including pain conditions and attention deficit hyperactivity disorder.

### Parasympathetic Effects

Drugs affecting parasympathetic functions can be classified into those that increase or decrease activity at postganglionic terminals. Parasympathetic postganglionic fibers release ACh, and the receptors on the targets are muscarinic receptors. There are several types of muscarinic receptors, M<sub>1</sub>–M<sub>5</sub>, but the drugs are not usually specific to the specific types. Parasympathetic drugs can be either muscarinic agonists or antagonists, or have indirect effects on the cholinergic system. Drugs that enhance cholinergic effects are called **parasympathomimetic drugs**, whereas those that inhibit cholinergic effects are referred to as **anticholinergic drugs**.

Pilocarpine is a nonspecific muscarinic agonist commonly used to treat disorders of the eye. It reverses mydriasis, such as is caused by phenylephrine, and can be administered after an eye exam. Along with constricting the pupil through the smooth muscle of the iris, pilocarpine will also cause the ciliary muscle to contract. This will open perforations at the base of the cornea, allowing for the drainage of aqueous humor from the anterior compartment of the eye and, therefore, reducing intraocular pressure related to glaucoma.

Atropine and scopolamine are part of a class of muscarinic antagonists that come from the *Atropa* genus of plants that include belladonna or deadly nightshade (Figure 15.15). The name of one of these plants, belladonna, refers to the fact that extracts from this plant were used cosmetically for dilating the pupil. The active chemicals from this plant block the muscarinic receptors in the iris and allow the pupil to dilate, which is considered attractive because it makes the eyes appear larger. Humans are instinctively attracted to anything with larger eyes, which comes from the fact that the ratio of eye-to-head size is different in infants (or baby animals) and can elicit an emotional response. The cosmetic use of belladonna extract was essentially acting on this response. Atropine is no longer used in this cosmetic capacity for reasons related to the other name for the plant, which is deadly nightshade. Suppression of parasympathetic function, especially when it becomes systemic, can be fatal. Autonomic regulation is disrupted and anticholinergic symptoms develop. The berries of this plant are highly toxic, but can be mistaken for other berries. The antidote for atropine or scopolamine poisoning is pilocarpine.



**FIGURE 15.15 Belladonna Plant** The plant from the genus *Atropa*, which is known as belladonna or deadly nightshade, was used cosmetically to dilate pupils, but can be fatal when ingested. The berries on the plant may seem attractive as a fruit, but they contain the same anticholinergic compounds as the rest of the plant.

### Sympathetic and Parasympathetic Effects of Different Drug Types

Drug type	Example(s)	Sympathetic effect	Parasympathetic effect	Overall result
Nicotinic agonists	Nicotine	Mimic ACh at preganglionic synapses, causing activation of postganglionic fibers and the release of norepinephrine onto the target organ	Mimic ACh at preganglionic synapses, causing activation of postganglionic fibers and the release of ACh onto the target organ	Most conflicting signals cancel each other out, but cardiovascular system is susceptible to hypertension and arrhythmias
Sympathomimetic drugs	Phenylephrine	Bind to adrenergic receptors or mimics sympathetic action in some other way	No effect	Increase sympathetic tone
Sympatholytic drugs	β-blockers such as propanolol or metoprolol; α-agonists such as clonidine	Block binding to adrenergic drug or decrease adrenergic signals	No effect	Increase parasympathetic tone
Parasympatho-mimetics/muscarinic agonists	Pilocarpine	No effect, except on sweat glands	Bind to muscarinic receptor, similar to ACh	Increase parasympathetic tone
Anticholinergics/muscarinic antagonists	Atropine, scopolamine, dimenhydrinate	No effect	Block muscarinic receptors and parasympathetic function	Increase sympathetic tone

TABLE 15.2

#### Disorders of the...

#### Autonomic Nervous System

Approximately 33 percent of people experience a mild problem with motion sickness, whereas up to 66 percent experience motion sickness under extreme conditions, such as being on a tossing boat with no view of the horizon. Connections between regions in the brain stem and the autonomic system result in the symptoms of nausea, cold sweats, and vomiting.

The part of the brain responsible for vomiting, or emesis, is known as the area postrema. It is located next to the fourth ventricle and is not restricted by the blood–brain barrier, which allows it to respond to chemicals in the bloodstream—namely, toxins that will stimulate emesis. There are significant connections between this area, the solitary nucleus, and the dorsal motor nucleus of the vagus nerve. These autonomic system and nuclei connections are associated with the symptoms of motion sickness.

Motion sickness is the result of conflicting information from the visual and vestibular systems. If motion is

perceived by the visual system without the complementary vestibular stimuli, or through vestibular stimuli without visual confirmation, the brain stimulates emesis and the associated symptoms. The area postrema, by itself, appears to be able to stimulate emesis in response to toxins in the blood, but it is also connected to the autonomic system and can trigger a similar response to motion.

Autonomic drugs are used to combat motion sickness. Though it is often described as a dangerous and deadly drug, scopolamine is used to treat motion sickness. A popular treatment for motion sickness is the transdermal scopolamine patch. Scopolamine is one of the substances derived from the *Atropa* genus along with atropine. At higher doses, those substances are thought to be poisonous and can lead to an extreme sympathetic syndrome. However, the transdermal patch regulates the release of the drug, and the concentration is kept very low so that the dangers are avoided. For those who are concerned about using “The Most Dangerous Drug,” as some websites will call it, antihistamines such as dimenhydrinate (Dramamine<sup>®</sup>) can be used.

### **INTERACTIVE LINK**

Watch this [video](http://openstax.org/l/3Dmovies) (<http://openstax.org/l/3Dmovies>) to learn about the side effects of 3-D movies. As discussed in this video, movies that are shot in 3-D can cause motion sickness, which elicits the autonomic symptoms of nausea and sweating. The disconnection between the perceived motion on the screen and the lack of any change in equilibrium stimulates these symptoms. Why do you think sitting close to the screen or right in the middle of the theater makes motion sickness during a 3-D movie worse?

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## Key Terms

**acetylcholine (ACh)** neurotransmitter that binds at a motor end-plate to trigger depolarization

**adrenal medulla** interior portion of the adrenal (or suprarenal) gland that releases epinephrine and norepinephrine into the bloodstream as hormones

**adrenergic** synapse where norepinephrine is released, which binds to  $\alpha$ - or  $\beta$ -adrenergic receptors

**afferent branch** component of a reflex arc that represents the input from a sensory neuron, for either a special or general sense

**agonist** any exogenous substance that binds to a receptor and produces a similar effect to the endogenous ligand

**alpha ( $\alpha$ )-adrenergic receptor** one of the receptors to which epinephrine and norepinephrine bind, which comes in two subtypes:  $\alpha_1$  and  $\alpha_2$

**antagonist** any exogenous substance that binds to a receptor and produces an opposing effect to the endogenous ligand

**anticholinergic drugs** drugs that interrupt or reduce the function of the parasympathetic system

**autonomic tone** tendency of an organ system to be governed by one division of the autonomic nervous system over the other, such as heart rate being lowered by parasympathetic input at rest

**baroreceptor** mechanoreceptor that senses the stretch of blood vessels to indicate changes in blood pressure

**beta ( $\beta$ )-adrenergic receptor** one of the receptors to which epinephrine and norepinephrine bind, which comes in three subtypes:  $\beta_1$ ,  $\beta_2$ , and  $\beta_3$

**cardiac accelerator nerves** preganglionic sympathetic fibers that cause the heart rate to increase when the cardiovascular center in the medulla initiates a signal

**cardiovascular center** region in the medulla that controls the cardiovascular system through cardiac accelerator nerves and vasomotor nerves, which are components of the sympathetic division of the autonomic nervous system

**celiac ganglion** one of the collateral ganglia of the sympathetic system that projects to the digestive system

**central neuron** specifically referring to the cell body of a neuron in the autonomic system that is located in the central nervous system, specifically the lateral horn of the spinal cord or a brain stem nucleus

**cholinergic** synapse at which acetylcholine is released and binds to the nicotinic or muscarinic receptor

**chromaffin cells** neuroendocrine cells of the adrenal medulla that release epinephrine and norepinephrine into the bloodstream as part of sympathetic system activity

**ciliary ganglion** one of the terminal ganglia of the parasympathetic system, located in the posterior orbit, axons from which project to the iris

**collateral ganglia** ganglia outside of the sympathetic chain that are targets of sympathetic preganglionic fibers, which are the celiac, inferior mesenteric, and superior mesenteric ganglia

**craniosacral system** alternate name for the parasympathetic division of the autonomic nervous system that is based on the anatomical location of central neurons in brain-stem nuclei and the lateral horn of the sacral spinal cord; also referred to as craniosacral outflow

**dorsal longitudinal fasciculus** major output pathway of the hypothalamus that descends through the gray matter of the brain stem and into the spinal cord

**dorsal nucleus of the vagus nerve** location of parasympathetic neurons that project through the vagus nerve to terminal ganglia in the thoracic and abdominal cavities

**Edinger-Westphal nucleus** location of parasympathetic neurons that project to the ciliary ganglion

**efferent branch** component of a reflex arc that represents the output, with the target being an effector, such as muscle or glandular tissue

**endogenous** describes substance made in the human body

**endogenous chemical** substance produced and released within the body to interact with a receptor protein

**epinephrine** signaling molecule released from the adrenal medulla into the bloodstream as part of the sympathetic response

**exogenous** describes substance made outside of the human body

**exogenous chemical** substance from a source outside the body, whether it be another organism such as a plant or from the synthetic processes of a laboratory, that binds to a transmembrane receptor protein

**fight-or-flight response** set of responses induced by sympathetic activity that lead to either fleeing a threat or standing up to it, which in the modern world is often associated with anxious feelings

**G protein-coupled receptor** membrane protein complex that consists of a receptor protein that binds to a signaling molecule—a G protein—that is

- activated by that binding and in turn activates an effector protein (enzyme) that creates a second-messenger molecule in the cytoplasm of the target cell
- ganglionic neuron** specifically refers to the cell body of a neuron in the autonomic system that is located in a ganglion
- gray rami communicantes** (singular = ramus communicans) unmyelinated structures that provide a short connection from a sympathetic chain ganglion to the spinal nerve that contains the postganglionic sympathetic fiber
- greater splanchnic nerve** nerve that contains fibers of the central sympathetic neurons that do not synapse in the chain ganglia but project onto the celiac ganglion
- inferior mesenteric ganglion** one of the collateral ganglia of the sympathetic system that projects to the digestive system
- intramural ganglia** terminal ganglia of the parasympathetic system that are found within the walls of the target effector
- lesser splanchnic nerve** nerve that contains fibers of the central sympathetic neurons that do not synapse in the chain ganglia but project onto the inferior mesenteric ganglion
- ligand-gated cation channel** ion channel, such as the nicotinic receptor, that is specific to positively charged ions and opens when a molecule such as a neurotransmitter binds to it
- limbic lobe** structures arranged around the edges of the cerebrum that are involved in memory and emotion
- long reflex** reflex arc that includes the central nervous system
- medial forebrain bundle** fiber pathway that extends anteriorly into the basal forebrain, passes through the hypothalamus, and extends into the brain stem and spinal cord
- mesenteric plexus** nervous tissue within the wall of the digestive tract that contains neurons that are the targets of autonomic preganglionic fibers and that project to the smooth muscle and glandular tissues in the digestive organ
- muscarinic receptor** type of acetylcholine receptor protein that is characterized by also binding to muscarine and is a metabotropic receptor
- mydriasis** dilation of the pupil; typically the result of disease, trauma, or drugs
- nicotinic receptor** type of acetylcholine receptor protein that is characterized by also binding to nicotine and is an ionotropic receptor
- norepinephrine** signaling molecule released as a neurotransmitter by most postganglionic sympathetic fibers as part of the sympathetic response, or as a hormone into the bloodstream from the adrenal medulla
- nucleus ambiguus** brain-stem nucleus that contains neurons that project through the vagus nerve to terminal ganglia in the thoracic cavity; specifically associated with the heart
- parasympathetic division** division of the autonomic nervous system responsible for restful and digestive functions
- parasympathomimetic drugs** drugs that enhance or mimic the function of the parasympathetic system
- paravertebral ganglia** autonomic ganglia superior to the sympathetic chain ganglia
- postganglionic fiber** axon from a ganglionic neuron in the autonomic nervous system that projects to and synapses with the target effector; sometimes referred to as a postganglionic neuron
- preganglionic fiber** axon from a central neuron in the autonomic nervous system that projects to and synapses with a ganglionic neuron; sometimes referred to as a preganglionic neuron
- prevertebral ganglia** autonomic ganglia that are anterior to the vertebral column and functionally related to the sympathetic chain ganglia
- referred pain** the conscious perception of visceral sensation projected to a different region of the body, such as the left shoulder and arm pain as a sign for a heart attack
- reflex arc** circuit of a reflex that involves a sensory input and motor output, or an afferent branch and an efferent branch, and an integrating center to connect the two branches
- rest and digest** set of functions associated with the parasympathetic system that lead to restful actions and digestion
- short reflex** reflex arc that does not include any components of the central nervous system
- somatic reflex** reflex involving skeletal muscle as the effector, under the control of the somatic nervous system
- superior cervical ganglion** one of the paravertebral ganglia of the sympathetic system that projects to the head
- superior mesenteric ganglion** one of the collateral ganglia of the sympathetic system that projects to the digestive system
- sympathetic chain ganglia** series of ganglia adjacent to the vertebral column that receive input from central sympathetic neurons
- sympathetic division** division of the autonomic nervous system associated with the fight-or-flight

response

**sympatholytic drug** drug that interrupts, or “lyses,” the function of the sympathetic system

**sympathomimetic drug** drug that enhances or mimics the function of the sympathetic system

**target effector** organ, tissue, or gland that will respond to the control of an autonomic or somatic or endocrine signal

**terminal ganglia** ganglia of the parasympathetic division of the autonomic system, which are located near or within the target effector, the latter also known as intramural ganglia

**thoracolumbar system** alternate name for the sympathetic division of the autonomic nervous system that is based on the anatomical location of central neurons in the lateral horn of the thoracic

and upper lumbar spinal cord

**varicosity** structure of some autonomic connections that is not a typical synaptic end bulb, but a string of swellings along the length of a fiber that makes a network of connections with the target effector

**vasomotor nerves** preganglionic sympathetic fibers that cause the constriction of blood vessels in response to signals from the cardiovascular center

**visceral reflex** reflex involving an internal organ as the effector, under the control of the autonomic nervous system

**white rami communicantes** (singular = ramus communicans) myelinated structures that provide a short connection from a sympathetic chain ganglion to the spinal nerve that contains the preganglionic sympathetic fiber

## Chapter Review

### 15.1 Divisions of the Autonomic Nervous System

The primary responsibilities of the autonomic nervous system are to regulate homeostatic mechanisms in the body, which is also part of what the endocrine system does. The key to understanding the autonomic system is to explore the response pathways—the output of the nervous system. The way we respond to the world around us, to manage the internal environment on the basis of the external environment, is divided between two parts of the autonomic nervous system. The sympathetic division responds to threats and produces a readiness to confront the threat or to run away: the fight-or-flight response. The parasympathetic division plays the opposite role. When the external environment does not present any immediate danger, a restful mode descends on the body, and the digestive system is more active.

The sympathetic output of the nervous system originates out of the lateral horn of the thoracolumbar spinal cord. An axon from one of these central neurons projects by way of the ventral spinal nerve root and spinal nerve to a sympathetic ganglion, either in the sympathetic chain ganglia or one of the collateral locations, where it synapses on a ganglionic neuron. These preganglionic fibers release ACh, which excites the ganglionic neuron through the nicotinic receptor. The axon from the ganglionic neuron—the postganglionic fiber—then projects to a target effector where it will release norepinephrine to bind to an adrenergic receptor, causing a change in the physiology of that organ in keeping with the broad, divergent sympathetic response. The postganglionic connections to sweat glands in the skin and blood vessels supplying

skeletal muscle are, however, exceptions; those fibers release ACh onto muscarinic receptors. The sympathetic system has a specialized preganglionic connection to the adrenal medulla that causes epinephrine and norepinephrine to be released into the bloodstream rather than exciting a neuron that contacts an organ directly. This hormonal component means that the sympathetic chemical signal can spread throughout the body very quickly and affect many organ systems at once.

The parasympathetic output is based in the brain stem and sacral spinal cord. Neurons from particular nuclei in the brain stem or from the lateral horn of the sacral spinal cord (preganglionic neurons) project to terminal (intramural) ganglia located close to or within the wall of target effectors. These preganglionic fibers also release ACh onto nicotinic receptors to excite the ganglionic neurons. The postganglionic fibers then contact the target tissues within the organ to release ACh, which binds to muscarinic receptors to induce rest-and-digest responses.

Signaling molecules utilized by the autonomic nervous system are released from axons and can be considered as either neurotransmitters (when they directly interact with the effector) or as hormones (when they are released into the bloodstream). The same molecule, such as norepinephrine, could be considered either a neurotransmitter or a hormone on the basis of whether it is released from a postganglionic sympathetic axon or from the adrenal gland. The synapses in the autonomic system are not always the typical type of connection first described in the neuromuscular junction. Instead of having synaptic end bulbs at the very end of an axonal fiber, they may have

swellings—called varicosities—along the length of a fiber so that it makes a network of connections within the target tissue.

## 15.2 Autonomic Reflexes and Homeostasis

Autonomic nervous system function is based on the visceral reflex. This reflex is similar to the somatic reflex, but the efferent branch is composed of two neurons. The central neuron projects from the spinal cord or brain stem to synapse on the ganglionic neuron that projects to the effector. The afferent branch of the somatic and visceral reflexes is very similar, as many somatic and special senses activate autonomic responses. However, there are visceral senses that do not form part of conscious perception. If a visceral sensation, such as cardiac pain, is strong enough, it will rise to the level of consciousness. However, the sensory homunculus does not provide a representation of the internal structures to the same degree as the surface of the body, so visceral sensations are often experienced as referred pain, such as feelings of pain in the left shoulder and arm in connection with a heart attack.

The role of visceral reflexes is to maintain a balance of function in the organ systems of the body. The two divisions of the autonomic system each play a role in effecting change, usually in competing directions. The sympathetic system increases heart rate, whereas the parasympathetic system decreases heart rate. The sympathetic system dilates the pupil of the eye, whereas the parasympathetic system constricts the pupil. The competing inputs can contribute to the resting tone of the organ system. Heart rate is normally under parasympathetic tone, whereas blood pressure is normally under sympathetic tone. The heart rate is slowed by the autonomic system at rest, whereas blood vessels retain a slight constriction at rest.

In a few systems of the body, the competing input from the two divisions is not the norm. The sympathetic tone of blood vessels is caused by the lack of parasympathetic input to the systemic circulatory system. Only certain regions receive parasympathetic input that relaxes the smooth muscle wall of the blood vessels. Sweat glands are another example, which only receive input from the sympathetic system.

## 15.3 Central Control

The autonomic system integrates sensory information and higher cognitive processes to generate output, which balances homeostatic mechanisms. The central autonomic structure is the hypothalamus, which coordinates sympathetic and parasympathetic efferent

pathways to regulate activities of the organ systems of the body. The majority of hypothalamic output travels through the medial forebrain bundle and the dorsal longitudinal fasciculus to influence brain stem and spinal components of the autonomic nervous system. The medial forebrain bundle also connects the hypothalamus with higher centers of the limbic system where emotion can influence visceral responses. The amygdala is a structure within the limbic system that influences the hypothalamus in the regulation of the autonomic system, as well as the endocrine system.

These higher centers have descending control of the autonomic system through brain stem centers, primarily in the medulla, such as the cardiovascular center. This collection of medullary nuclei regulates cardiac function, as well as blood pressure. Sensory input from the heart, aorta, and carotid sinuses project to these regions of the medulla. The solitary nucleus increases sympathetic tone of the cardiovascular system through the cardiac accelerator and vasmotor nerves. The nucleus ambiguus and the dorsal motor nucleus both contribute fibers to the vagus nerve, which exerts parasympathetic control of the heart by decreasing heart rate.

## 15.4 Drugs that Affect the Autonomic System

The autonomic system is affected by a number of exogenous agents, including some that are therapeutic and some that are illicit. These drugs affect the autonomic system by mimicking or interfering with the endogenous agents or their receptors. A survey of how different drugs affect autonomic function illustrates the role that the neurotransmitters and hormones play in autonomic function. Drugs can be thought of as chemical tools to effect changes in the system with some precision, based on where those drugs are effective.

Nicotine is not a drug that is used therapeutically, except for smoking cessation. When it is introduced into the body via products, it has broad effects on the autonomic system. Nicotine carries a risk for cardiovascular disease because of these broad effects. The drug stimulates both sympathetic and parasympathetic ganglia at the preganglionic fiber synapse. For most organ systems in the body, the competing input from the two postganglionic fibers will essentially cancel each other out. However, for the cardiovascular system, the results are different. Because there is essentially no parasympathetic influence on blood pressure for the entire body, the sympathetic input is increased by nicotine, causing an

increase in blood pressure. Also, the influence that the autonomic system has on the heart is not the same as for other systems. Other organs have smooth muscle or glandular tissue that is activated or inhibited by the autonomic system. Cardiac muscle is intrinsically active and is modulated by the autonomic system. The contradictory signals do not just cancel each other out, they alter the regularity of the heart rate and can cause arrhythmias. Both hypertension and arrhythmias are risk factors for heart disease.

Other drugs affect one division of the autonomic system or the other. The sympathetic system is affected by drugs that mimic the actions of adrenergic molecules (norepinephrine and epinephrine) and are

called sympathomimetic drugs. Drugs such as phenylephrine bind to the adrenergic receptors and stimulate target organs just as sympathetic activity would. Other drugs are sympatholytic because they block adrenergic activity and cancel the sympathetic influence on the target organ. Drugs that act on the parasympathetic system also work by either enhancing the postganglionic signal or blocking it. A muscarinic agonist (or parasympathomimetic drug) acts just like ACh released by the parasympathetic postganglionic fiber. Anticholinergic drugs block muscarinic receptors, suppressing parasympathetic interaction with the organ.

## Interactive Link Questions

- Watch this [video](http://openstax.org/l/fightflight) (<http://openstax.org/l/fightflight>) to learn more about adrenaline and the fight-or-flight response. When someone is said to have a rush of adrenaline, the image of bungee jumpers or skydivers usually comes to mind. But adrenaline, also known as epinephrine, is an important chemical in coordinating the body's fight-or-flight response. In this video, you look inside the physiology of the fight-or-flight response, as envisioned for a firefighter. His body's reaction is the result of the sympathetic division of the autonomic nervous system causing system-wide changes as it prepares for extreme responses. What two changes does adrenaline bring about to help the skeletal muscle response?
- Watch this [video](http://openstax.org/l/nervsystem1) (<http://openstax.org/l/nervsystem1>) to learn more about the nervous system. As described in this video, the nervous system has a way to deal with threats and stress that is separate from the conscious control of the somatic nervous system. The system comes from a time when threats were about survival, but in the modern age, these responses become part of stress and anxiety. This video describes how the autonomic system is only part of the response to threats, or stressors. What other organ system gets involved, and what part of the brain coordinates the two systems for the entire response, including epinephrine (adrenaline) and cortisol?
- Read this [article](http://openstax.org/l/strokespell) (<http://openstax.org/l/strokespell>) to learn about a teenager who experiences a series of spells that suggest a stroke. He undergoes endless tests and seeks input from multiple doctors. In the end, one expert, one question, and a simple blood pressure cuff answers the question. Why would the heart have to beat faster when the teenager changes his body position from lying down to sitting, and then to standing?
- Watch this [video](http://openstax.org/l/pupillary) (<http://openstax.org/l/pupillary>) to learn about the pupillary reflexes. The pupillary light reflex involves sensory input through the optic nerve and motor response through the oculomotor nerve to the ciliary ganglion, which projects to the circular fibers of the iris. As shown in this short animation, pupils will constrict to limit the amount of light falling on the retina under bright lighting conditions. What constitutes the afferent and efferent branches of the competing reflex (dilation)?
- Watch this [video](http://openstax.org/l/emotions) (<http://openstax.org/l/emotions>) to learn about physical responses to emotion. The autonomic system, which is important for regulating the homeostasis of the organ systems, is also responsible for our physiological responses to emotions such as fear. The video summarizes the extent of the body's reactions and describes several effects of the autonomic system in response to fear. On the basis of what you have already studied about autonomic function, which effect would you expect to be associated with parasympathetic, rather than sympathetic, activity?

- 6.** Watch this [video](http://openstax.org/l/3Dmovies) (<http://openstax.org/l/3Dmovies>) to learn about the side effects of 3-D movies. As discussed in this video, movies that are shot in 3-D can cause motion sickness, which elicits the autonomic symptoms of nausea and sweating. The disconnection between the perceived motion on the screen and the lack of any change in equilibrium stimulates these symptoms. Why do you think sitting close to the screen or right in the middle of the theater makes motion sickness during a 3-D movie worse?

## Review Questions

- 7.** Which of these physiological changes would *not* be considered part of the sympathetic fight-or-flight response?
  - a. increased heart rate
  - b. increased sweating
  - c. dilated pupils
  - d. increased stomach motility
- 8.** Which type of fiber could be considered the longest?
  - a. preganglionic parasympathetic
  - b. preganglionic sympathetic
  - c. postganglionic parasympathetic
  - d. postganglionic sympathetic
- 9.** Which signaling molecule is *most likely* responsible for an increase in digestive activity?
  - a. epinephrine
  - b. norepinephrine
  - c. acetylcholine
  - d. adrenaline
- 10.** Which of these cranial nerves contains preganglionic parasympathetic fibers?
  - a. optic, CN II
  - b. facial, CN VII
  - c. trigeminal, CN V
  - d. hypoglossal, CN XII
- 11.** Which of the following is *not* a target of a sympathetic preganglionic fiber?
  - a. intermural ganglion
  - b. collateral ganglion
  - c. adrenal gland
  - d. chain ganglion
- 12.** Which of the following represents a sensory input that is *not* part of both the somatic and autonomic systems?
  - a. vision
  - b. taste
  - c. baroreception
  - d. proprioception
- 13.** What is the term for a reflex that does *not* include a CNS component?
  - a. long reflex
  - b. visceral reflex
  - c. somatic reflex
  - d. short reflex
- 14.** What neurotransmitter will result in constriction of the pupil?
  - a. norepinephrine
  - b. acetylcholine
  - c. epinephrine
  - d. serotonin
- 15.** What gland produces a secretion that causes fight-or-flight responses in effectors?
  - a. adrenal medulla
  - b. salivatory gland
  - c. reproductive gland
  - d. thymus
- 16.** Which of the following is an incorrect pairing?
  - a. norepinephrine dilates the pupil
  - b. epinephrine increases blood pressure
  - c. acetylcholine decreases digestion
  - d. norepinephrine increases heart rate
- 17.** Which of these locations in the forebrain is the master control center for homeostasis through the autonomic and endocrine systems?
  - a. hypothalamus
  - b. thalamus
  - c. amygdala
  - d. cerebral cortex

- 18.** Which nerve projects to the hypothalamus to indicate the level of light stimuli in the retina?
- glossopharyngeal
  - oculomotor
  - optic
  - vagus
- 19.** What region of the limbic lobe is responsible for generating stress responses via the hypothalamus?
- hippocampus
  - amygdala
  - mammillary bodies
  - prefrontal cortex
- 20.** What is another name for the preganglionic sympathetic fibers that project to the heart?
- solitary tract
  - vasomotor nerve
  - vagus nerve
  - cardiac accelerator nerve
- 21.** What central fiber tract connects forebrain and brain stem structures with the hypothalamus?
- cardiac accelerator nerve
  - medial forebrain bundle
  - dorsal longitudinal fasciculus
  - corticospinal tract
- 22.** A drug that affects both divisions of the autonomic system is going to bind to, or block, which type of neurotransmitter receptor?
- nicotinic
  - muscarinic
  - $\alpha$ -adrenergic
  - $\beta$ -adrenergic
- 23.** A drug is called an agonist if it \_\_\_\_\_.
- blocks a receptor
  - interferes with neurotransmitter reuptake
  - acts like the endogenous neurotransmitter by binding to its receptor
  - blocks the voltage-gated calcium ion channel
- 24.** Which type of drug would be an antidote to atropine poisoning?
- nicotinic agonist
  - anticholinergic
  - muscarinic agonist
  - $\alpha$ -blocker
- 25.** Which kind of drug would have anti-anxiety effects?
- nicotinic agonist
  - anticholinergic
  - muscarinic agonist
  - $\alpha$ -blocker
- 26.** Which type of drug could be used to treat asthma by opening airways wider?
- sympatholytic drug
  - sympathomimetic drug
  - anticholinergic drug
  - parasympathomimetic drug

## Critical Thinking Questions

- 27.** In the context of a lioness hunting on the savannah, why would the sympathetic system *not* activate the digestive system?
- 28.** A target effector, such as the heart, receives input from the sympathetic and parasympathetic systems. What is the actual difference between the sympathetic and parasympathetic divisions at the level of those connections (i.e., at the synapse)?
- 29.** Damage to internal organs will present as pain associated with a particular surface area of the body. Why would something like irritation to the diaphragm, which is between the thoracic and abdominal cavities, feel like pain in the shoulder or neck?
- 30.** Medical practice is paying more attention to the autonomic system in considering disease states. Why would autonomic tone be important in considering cardiovascular disease?
- 31.** Horner's syndrome is a condition that presents with changes in one eye, such as pupillary constriction and dropping of eyelids, as well as decreased sweating in the face. Why could a tumor in the thoracic cavity have an effect on these autonomic functions?
- 32.** The cardiovascular center is responsible for regulating the heart and blood vessels through homeostatic mechanisms. What tone does each component of the cardiovascular system have? What connections does the cardiovascular center invoke to keep these two systems in their resting tone?

- 33.** Why does smoking increase the risk of heart disease? Provide two reasons based on autonomic function.
- 34.** Why might topical, cosmetic application of atropine or scopolamine from the belladonna plant not cause fatal poisoning, as would occur with ingestion of the plant?



# CHAPTER 16

## The Neurological Exam



**Figure 16.1** Neurological Exam Health care professionals, such as this air force nurse, can rapidly assess the neurological functions of a patient using the neurological exam. One part of the exam is the inspection of the oral cavity and pharynx, which enables the doctor to not only inspect the tissues for signs of infection, but also provides a means to test the functions of the cranial nerves associated with the oral cavity. (credit: U.S. Department of Defense / AMISOM Public Information/Flickr)

### CHAPTER OBJECTIVES

After studying this chapter, you will be able to:

- Describe the major sections of the neurological exam
- Outline the benefits of rapidly assessing neurological function
- Relate anatomical structures of the nervous system to specific functions
- Diagram the connections of the nervous system to the musculature and integument involved in primary sensorimotor responses
- Compare and contrast the somatic and visceral reflexes with respect to how they are assessed through the neurological exam

**INTRODUCTION** A man arrives at the hospital after feeling faint and complaining of a “pins-and-needles” feeling all along one side of his body. The most likely explanation is that he has suffered a stroke, which has caused a loss of oxygen to a particular part of the central nervous system (CNS). The problem is finding where in the entire nervous system the stroke has occurred. By checking reflexes, sensory responses, and motor control, a health care provider can focus on what abilities the patient may have lost as a result of the stroke and can use this information to determine where the injury occurred. In the emergency department of the hospital, this kind of rapid assessment of neurological function is key to treating trauma to the nervous system. In the classroom, the neurological exam is a valuable tool for learning the anatomy and physiology of the nervous system because it allows you to relate the functions of the system to particular locations in the nervous system.

As a student of anatomy and physiology, you may be planning to go into an allied health field, perhaps nursing or physical therapy. You could be in the emergency department treating a patient such as the one just described. An important part of this course is to understand the nervous system. This can be especially challenging because you need to learn about the nervous system using your own nervous system. The first chapter in this unit about the nervous system began with a quote: “If the human brain were simple enough for us to understand, we would be too simple to understand it.” However, you are being asked to understand aspects of it. A healthcare provider can pinpoint problems with the nervous system in minutes by running through the series of tasks to test neurological function that are described in this chapter. You can use the same approach, though not as quickly, to learn about neurological function and its relationship to the structures of the nervous system.

Nervous tissue is different from other tissues in that it is not classified into separate tissue types. It does contain two types of cells, neurons and glia, but it is all just nervous tissue. White matter and gray matter are not types of

nervous tissue, but indications of different specializations within the nervous tissue. However, not all nervous tissue performs the same function. Furthermore, specific functions are not wholly localized to individual brain structures in the way that other bodily functions occur strictly within specific organs. In the CNS, we must consider the connections between cells over broad areas, not just the function of cells in one particular nucleus or region. In a broad sense, the nervous system is responsible for the majority of electrochemical signaling in the body, but the use of those signals is different in various regions.

The nervous system is made up of the brain and spinal cord as the central organs, and the ganglia and nerves as organs in the periphery. The brain and spinal cord can be thought of as a collection of smaller organs, most of which would be the nuclei (such as the oculomotor nuclei), but white matter structures play an important role (such as the corpus callosum). Studying the nervous system requires an understanding of the varied physiology of the nervous system. For example, the hypothalamus plays a very different role than the visual cortex. The neurological exam provides a way to elicit behavior that represents those varied functions.

## 16.1 Overview of the Neurological Exam

### LEARNING OBJECTIVES

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

- List the major sections of the neurological exam
- Explain the connection between location and function in the nervous system
- Explain the benefit of a rapid assessment for neurological function in a clinical setting
- List the causes of neurological deficits
- Describe the different ischemic events in the nervous system

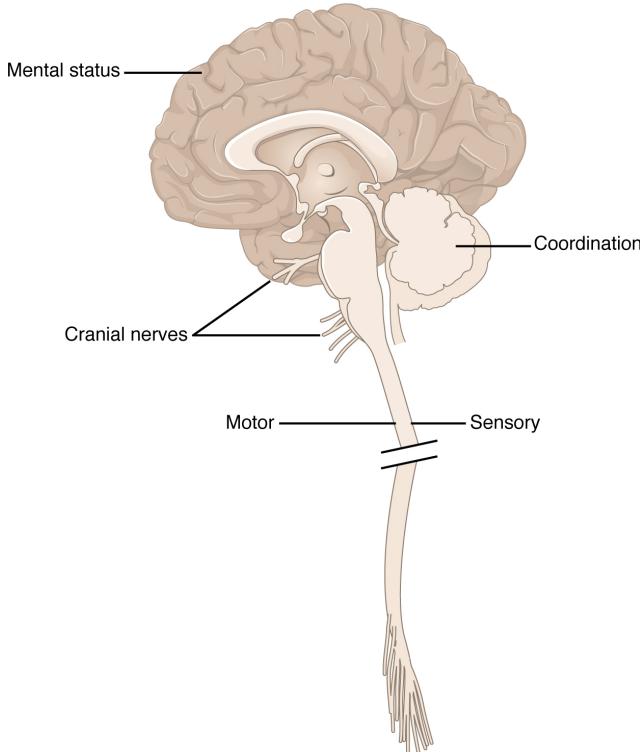
The **neurological exam** is a clinical assessment tool used to determine what specific parts of the CNS are affected by damage or disease. It can be performed in a short time—sometimes as quickly as 5 minutes—to establish neurological function. In the emergency department, this rapid assessment can make the difference with respect to proper treatment and the extent of recovery that is possible.

The exam is a series of subtests separated into five major sections. The first of these is the **mental status exam**, which assesses the higher cognitive functions such as memory, orientation, and language. Then there is the **cranial nerve exam**, which tests the function of the 12 cranial nerves and, therefore, the central and peripheral structures associated with them. The cranial nerve exam tests the sensory and motor functions of each of the nerves, as applicable. Two major sections, the **sensory exam** and the **motor exam**, test the sensory and motor functions associated with spinal nerves. Finally, the **coordination exam** tests the ability to perform complex and coordinated movements. The **gait exam**, which is often considered a sixth major exam, specifically assesses the motor function of walking and can be considered part of the coordination exam because walking is a coordinated movement.

### Neuroanatomy and the Neurological Exam

**Localization of function** is the concept that circumscribed locations are responsible for specific functions. The neurological exam highlights this relationship. For example, the cognitive functions that are assessed in the mental status exam are based on functions in the cerebrum, mostly in the cerebral cortex. Several of the subtests examine language function. Deficits in neurological function uncovered by these examinations usually point to damage to the left cerebral cortex. In the majority of individuals, language function is localized to the left hemisphere between the superior temporal lobe and the posterior frontal lobe, including the intervening connections through the inferior parietal lobe.

The five major sections of the neurological exam are related to the major regions of the CNS ([Figure 16.2](#)). The mental status exam assesses functions related to the cerebrum. The cranial nerve exam is for the nerves that connect to the diencephalon and brain stem (as well as the olfactory connections to the forebrain). The coordination exam and the related gait exam primarily assess the functions of the cerebellum. The motor and sensory exams are associated with the spinal cord and its connections through the spinal nerves.



**FIGURE 16.2 Anatomical Underpinnings of the Neurological Exam** The different regions of the CNS relate to the major sections of the neurological exam: the mental status exam, cranial nerve exam, sensory exam, motor exam, and coordination exam (including the gait exam).

Part of the power of the neurological exam is this link between structure and function. Testing the various functions represented in the exam allows an accurate estimation of where the nervous system may be damaged. Consider the patient described in the chapter introduction. In the emergency department, he is given a quick exam to find where the deficit may be localized. Knowledge of where the damage occurred will lead to the most effective therapy.

In rapid succession, he is asked to smile, raise his eyebrows, stick out his tongue, and shrug his shoulders. The doctor tests muscular strength by providing resistance against his arms and legs while he tries to lift them. With his eyes closed, he has to indicate when he feels the tip of a pen touch his legs, arms, fingers, and face. He follows the tip of a pen as the doctor moves it through the visual field and finally toward his face. A formal mental status exam is not needed at this point; the patient will demonstrate any possible deficits in that area during normal interactions with the interviewer. If cognitive or language deficits are apparent, the interviewer can pursue mental status in more depth. All of this takes place in less than 5 minutes. The patient reports that he feels pins and needles in his left arm and leg, and has trouble feeling the tip of the pen when he is touched on those limbs. This suggests a problem with the sensory systems between the spinal cord and the brain. The emergency department has a lead to follow before a CT scan is performed. He is put on aspirin therapy to limit the possibility of blood clots forming, in case the cause is an **embolus**—an obstruction such as a blood clot that blocks the flow of blood in an artery or vein.

### **INTERACTIVE LINK**

Watch this [video](http://openstax.org/l/neuroexam) (<http://openstax.org/l/neuroexam>) to see a demonstration of the neurological exam—a series of tests that can be performed rapidly when a patient is initially brought into an emergency department. The exam can be repeated on a regular basis to keep a record of how and if neurological function changes over time. In what order were the sections of the neurological exam tested in this video, and which section seemed to be left out?

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### **Causes of Neurological Deficits**

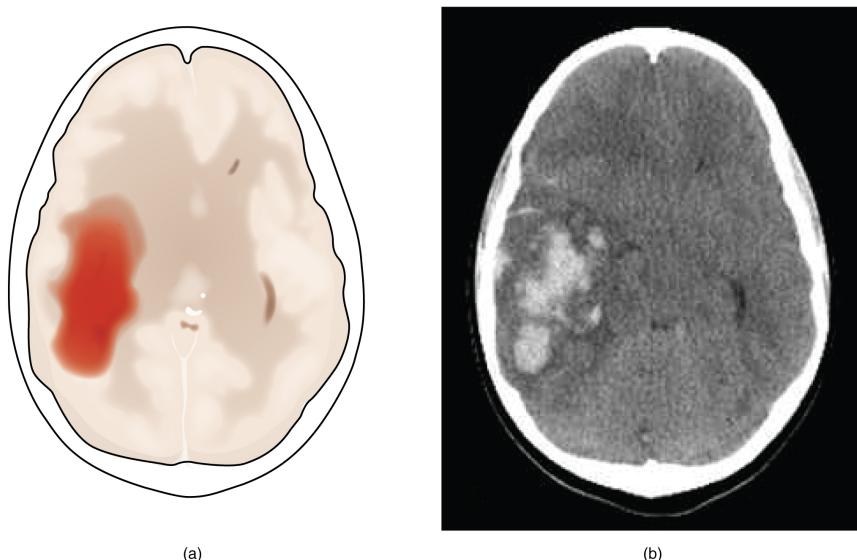
Damage to the nervous system can be limited to individual structures or can be distributed across broad areas of the brain and spinal cord. Localized, limited injury to the nervous system is most often the result of circulatory problems. Neurons are very sensitive to oxygen deprivation and will start to deteriorate within 1 or 2 minutes, and

permanent damage (cell death) could result within a few hours. The loss of blood flow to part of the brain is known as a **stroke**, or a cerebrovascular accident (CVA).

There are two main types of stroke, depending on how the blood supply is compromised: ischemic and hemorrhagic. An **ischemic stroke** is the loss of blood flow to an area because vessels are blocked or narrowed. This is often caused by an embolus, which may be a blood clot or fat deposit. Ischemia may also be the result of thickening of the blood vessel wall, or a drop in blood volume in the brain known as **hypovolemia**.

A related type of CVA is known as a **transient ischemic attack (TIA)**, which is similar to a stroke although it does not last as long. The diagnostic definition of a stroke includes effects that last at least 24 hours. Any stroke symptoms that are resolved within a 24-hour period because of restoration of adequate blood flow are classified as a TIA.

A **hemorrhagic stroke** is bleeding into the brain because of a damaged blood vessel. Accumulated blood fills a region of the cranial vault and presses against the tissue in the brain (Figure 16.3). Physical pressure on the brain can cause the loss of function, as well as the squeezing of local arteries resulting in compromised blood flow beyond the site of the hemorrhage. As blood pools in the nervous tissue and the vasculature is damaged, the blood-brain barrier can break down and allow additional fluid to accumulate in the region, which is known as **edema**.



**FIGURE 16.3 Hemorrhagic Stroke** (a) A hemorrhage into the tissue of the cerebrum results in a large accumulation of blood with an additional edema in the adjacent tissue. The hemorrhagic area causes the entire brain to be disfigured as suggested here by the lateral ventricles being squeezed into the opposite hemisphere. (b) A CT scan shows an intraparenchymal hemorrhage within the parietal lobe. (credit b: James Heilman)

Whereas hemorrhagic stroke may involve bleeding into a large region of the CNS, such as into the deep white matter of a cerebral hemisphere, other events can cause widespread damage and loss of neurological functions. Infectious diseases can lead to loss of function throughout the CNS as components of nervous tissue, specifically astrocytes and microglia, react to the disease. Blunt force trauma, such as from a motor vehicle accident, can physically damage the CNS.

A class of disorders that affect the nervous system are the neurodegenerative diseases: Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), Creutzfeld–Jacob disease, multiple sclerosis (MS), and other disorders that are the result of nervous tissue degeneration. In diseases like Alzheimer's, Parkinson's, or ALS, neurons die; in diseases like MS, myelin is affected. Some of these disorders affect motor function, and others present with dementia. How patients with these disorders perform in the neurological exam varies, but is often broad in its effects, such as memory deficits that compromise many aspects of the mental status exam, or movement deficits that compromise aspects of the cranial nerve exam, the motor exam, or the coordination exam. The causes of these disorders are also varied. Some are the result of genetics, such as Huntington's disease, or the result of autoimmunity, such as MS; others are not entirely understood, such as Alzheimer's and Parkinson's diseases. Current research suggests that many of these diseases are related in how the degeneration takes place and may be treated by common therapies.

Finally, a common cause of neurological changes is observed in developmental disorders. Whether the result of genetic factors or the environment during development, there are certain situations that result in neurological functions being different from the expected norms. Developmental disorders are difficult to define because they are caused by defects that existed in the past and disrupted the normal development of the CNS. These defects probably involve multiple environmental and genetic factors—most of the time, we don't know what the cause is other than that it is more complex than just one factor. Furthermore, each defect on its own may not be a problem, but when several are added together, they can disrupt growth processes that are not well understood in the first place. For instance, it is possible for a stroke to damage a specific region of the brain and lead to the loss of the ability to recognize faces (prosopagnosia). The link between cell death in the fusiform gyrus and the symptom is relatively easy to understand. In contrast, similar deficits can be seen in children with the developmental disorder, autism spectrum disorder (ASD). However, these children do not lack a fusiform gyrus, nor is there any damage or defect visible to this brain region. We conclude, rather poorly, that this brain region is not connected properly to other brain regions.

Infection, trauma, and congenital disorders can all lead to significant signs, as identified through the neurological exam. It is important to differentiate between an acute event, such as stroke, and a chronic or global condition such as blunt force trauma. Responses seen in the neurological exam can help. A loss of language function observed in all its aspects is more likely a global event as opposed to a discrete loss of one function, such as not being able to say certain types of words. A concern, however, is that a specific function—such as controlling the muscles of speech—may mask other language functions. The various subtests within the mental status exam can address these finer points and help clarify the underlying cause of the neurological loss.

### **INTERACTIVE LINK**

Watch this [video \(<http://openstax.org/l/neuroexam2>\)](http://openstax.org/l/neuroexam2) for an introduction to the neurological exam. Studying the neurological exam can give insight into how structure and function in the nervous system are interdependent. This is a tool both in the clinic and in the classroom, but for different reasons. In the clinic, this is a powerful but simple tool to assess a patient's neurological function. In the classroom, it is a different way to think about the nervous system. Though medical technology provides noninvasive imaging and real-time functional data, the presenter says these cannot replace the history at the core of the medical examination. What does history mean in the context of medical practice?

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## 16.2 The Mental Status Exam

### LEARNING OBJECTIVES

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

- Describe the relationship of mental status exam results to cerebral functions
- Explain the categorization of regions of the cortex based on anatomy and physiology
- Differentiate between primary, association, and integration areas of the cerebral cortex
- Provide examples of localization of function related to the cerebral cortex

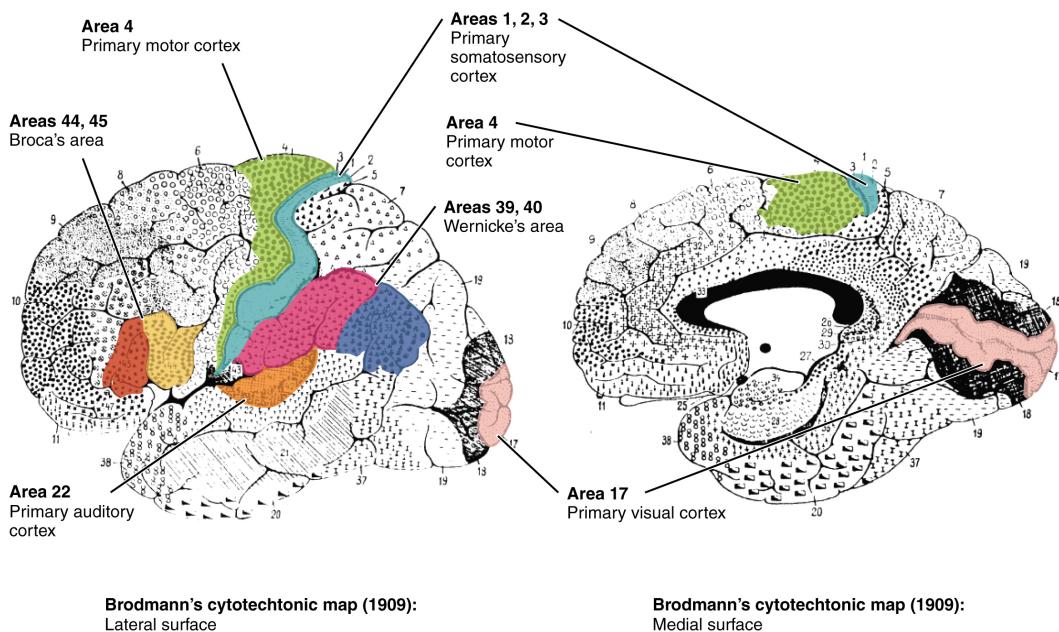
In the clinical setting, the set of subtests known as the mental status exam helps us understand the relationship of the brain to the body. Ultimately, this is accomplished by assessing behavior. Tremors related to intentional movements, incoordination, or the neglect of one side of the body can be indicative of failures of the connections of the cerebrum either within the hemispheres, or from the cerebrum to other portions of the nervous system. There is no strict test for what the cerebrum does alone, but rather in what it does through its control of the rest of the CNS, the peripheral nervous system (PNS), and the musculature.

Sometimes eliciting a behavior is as simple as asking a question. Asking a patient to state their name is not only to verify that the file folder in a health care provider's hands is the correct one, but also to be sure that the patient is aware, oriented, and capable of interacting with another person. If the answer to "What is your name?" is "Santa Claus," the person may have a problem understanding reality. If the person just stares at the examiner with a confused look on their face, the person may have a problem understanding or producing speech.

## Functions of the Cerebral Cortex

The cerebrum is the seat of many of the higher mental functions, such as memory and learning, language, and conscious perception, which are the subjects of subtests of the mental status exam. The cerebral cortex is the thin layer of gray matter on the outside of the cerebrum. On average, it is approximately 2.55 mm thick and highly folded to fit within the limited space of the cranial vault. These higher functions are distributed across various regions of the cortex, and specific locations can be said to be responsible for particular functions. There is a limited set of regions, for example, that are involved in language function, and they can be subdivided on the basis of the particular part of language function that each governs.

The basis for parceling out areas of the cortex and attributing them to various functions has its root in pure anatomical underpinnings. The German neurologist and histologist Korbinian Brodmann, who made a careful study of the **cytoarchitecture** of the cerebrum around the turn of the nineteenth century, described approximately 50 regions of the cortex that differed enough from each other to be considered separate areas (Figure 16.4). Brodmann made preparations of many different regions of the cerebral cortex to view with a microscope. He compared the size, shape, and number of neurons to find anatomical differences in the various parts of the cerebral cortex. Continued investigation into these anatomical areas over the subsequent 100 or more years has demonstrated a strong correlation between the structures and the functions attributed to those structures. For example, the first three areas in Brodmann's list—which are in the postcentral gyrus—compose the primary somatosensory cortex. Within this area, finer separation can be made on the basis of the concept of the sensory homunculus, as well as the different submodalities of somatosensation such as touch, vibration, pain, temperature, or proprioception. Today, we more frequently refer to these regions by their function (i.e., primary sensory cortex) than by the number Brodmann assigned to them, but in some situations the use of Brodmann numbers persists.

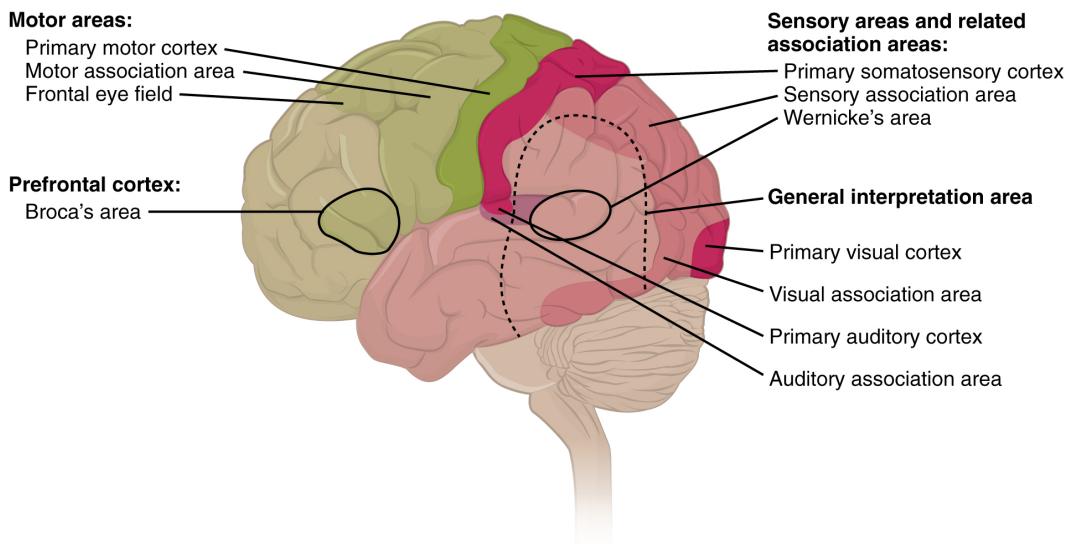


**FIGURE 16.4 Brodmann's Areas of the Cerebral Cortex** On the basis of cytoarchitecture, the anatomist Korbinian Brodmann described the extensive array of cortical regions, as illustrated in this figure. Subsequent investigations found that these areas corresponded very well to functional differences in the cerebral cortex. (credit: modification of work by "Looie496"/Wikimedia Commons, based on original work by Korbinian Brodmann)

Area 17, as Brodmann described it, is also known as the primary visual cortex. Adjacent to that are areas 18 and 19, which constitute subsequent regions of visual processing. Area 22 is the primary auditory cortex, and it is followed by area 23, which further processes auditory information. Area 4 is the primary motor cortex in the precentral gyrus, whereas area 6 is the premotor cortex. These areas suggest some specialization within the cortex for functional processing, both in sensory and motor regions. The fact that Brodmann's areas correlate so closely to functional localization in the cerebral cortex demonstrates the strong link between structure and function in these regions.

Areas 1, 2, 3, 4, 17, and 22 are each described as primary cortical areas. The adjoining regions are each referred to as association areas. Primary areas are where sensory information is initially received from the thalamus for

conscious perception, or—in the case of the primary motor cortex—where descending commands are sent down to the brain stem or spinal cord to execute movements ([Figure 16.5](#)).



**FIGURE 16.5 Types of Cortical Areas** The cerebral cortex can be described as containing three types of processing regions: primary, association, and integration areas. The primary cortical areas are where sensory information is initially processed, or where motor commands emerge to go to the brain stem or spinal cord. Association areas are adjacent to primary areas and further process the modality-specific input. Multimodal integration areas are found where the modality-specific regions meet; they can process multiple modalities together or different modalities on the basis of similar functions, such as spatial processing in vision or somatosensation.

A number of other regions, which extend beyond these primary or association areas of the cortex, are referred to as integrative areas. These areas are found in the spaces between the domains for particular sensory or motor functions, and they integrate multisensory information, or process sensory or motor information in more complex ways. Consider, for example, the posterior parietal cortex that lies between the somatosensory cortex and visual cortex regions. This has been ascribed to the coordination of visual and motor functions, such as reaching to pick up a glass. The somatosensory function that would be part of this is the proprioceptive feedback from moving the arm and hand. The weight of the glass, based on what it contains, will influence how those movements are executed.

## Cognitive Abilities

Assessment of cerebral functions is directed at cognitive abilities. The abilities assessed through the mental status exam can be separated into four groups: orientation and memory, language and speech, sensorium, and judgment and abstract reasoning.

### Orientation and Memory

Orientation is the patient's awareness of their immediate circumstances. It is awareness of time, not in terms of the clock, but of the date and what is occurring around the patient. It is awareness of place, such that a patient should know where they are and why. It is also awareness of who the patient is—recognizing personal identity and being able to relate that to the examiner. The initial tests of orientation are based on the questions, “Do you know what the date is?” or “Do you know where you are?” or “What is your name?” Further understanding of a patient’s awareness of orientation can come from questions that address remote memory, such as “Who is the President of the United States?”, or asking what happened on a specific date.

There are also specific tasks to address memory. One is the three-word recall test. The patient is given three words to recall, such as book, clock, and shovel. After a short interval, during which other parts of the interview continue, the patient is asked to recall the three words. Other tasks that assess memory—aside from those related to orientation—have the patient recite the months of the year in reverse order to avoid the overlearned sequence and focus on the memory of the months in an order, or to spell common words backwards, or to recite a list of numbers back.

Memory is largely a function of the temporal lobe, along with structures beneath the cerebral cortex such as the hippocampus and the amygdala. The storage of memory requires these structures of the medial temporal lobe. A

famous case of a man who had both medial temporal lobes removed to treat intractable epilepsy provided insight into the relationship between the structures of the brain and the function of memory.

Henry Molaison, who was referred to as patient HM when he was alive, had epilepsy localized to both of his medial temporal lobes. In 1953, a bilateral lobectomy was performed that alleviated the epilepsy but resulted in the inability for HM to form new memories—a condition called **anterograde amnesia**. HM was able to recall most events from before his surgery, although there was a partial loss of earlier memories, which is referred to as **retrograde amnesia**. HM became the subject of extensive studies into how memory works. What he was unable to do was form new memories of what happened to him, what are now called **episodic memory**. Episodic memory is autobiographical in nature, such as remembering riding a bicycle as a child around the neighborhood, as opposed to the **procedural memory** of how to ride a bike. HM also retained his **short-term memory**, such as what is tested by the three-word task described above. After a brief period, those memories would dissipate or decay and not be stored in the long-term because the medial temporal lobe structures were removed.

The difference in short-term, procedural, and episodic memory, as evidenced by patient HM, suggests that there are different parts of the brain responsible for those functions. The long-term storage of episodic memory requires the hippocampus and related medial temporal structures, and the location of those memories is in the multimodal integration areas of the cerebral cortex. However, short-term memory—also called working or active memory—is localized to the prefrontal lobe. Because patient HM had only lost his medial temporal lobe—and lost very little of his previous memories, and did not lose the ability to form new short-term memories—it was concluded that the function of the hippocampus, and adjacent structures in the medial temporal lobe, is to move (or consolidate) short-term memories (in the pre-frontal lobe) to long-term memory (in the temporal lobe).

The prefrontal cortex can also be tested for the ability to organize information. In one subtest of the mental status exam called set generation, the patient is asked to generate a list of words that all start with the same letter, but not to include proper nouns or names. The expectation is that a person can generate such a list of at least 10 words within 1 minute. Many people can likely do this much more quickly, but the standard separates the accepted normal from those with compromised prefrontal cortices.

## **INTERACTIVE LINK**

Read this [article](http://openstax.org/l/3word) (<http://openstax.org/l/3word>) to learn about a young man who texts his fiancée in a panic as he finds that he is having trouble remembering things. At the hospital, a neurologist administers the mental status exam, which is mostly normal except for the three-word recall test. The young man could not recall them even 30 seconds after hearing them and repeating them back to the doctor. An undiscovered mass in the mediastinum region was found to be Hodgkin's lymphoma, a type of cancer that affects the immune system and likely caused antibodies to attack the nervous system. The patient eventually regained his ability to remember, though the events in the hospital were always elusive. Considering that the effects on memory were temporary, but resulted in the loss of the specific events of the hospital stay, what regions of the brain were likely to have been affected by the antibodies and what type of memory does that represent?

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### **Language and Speech**

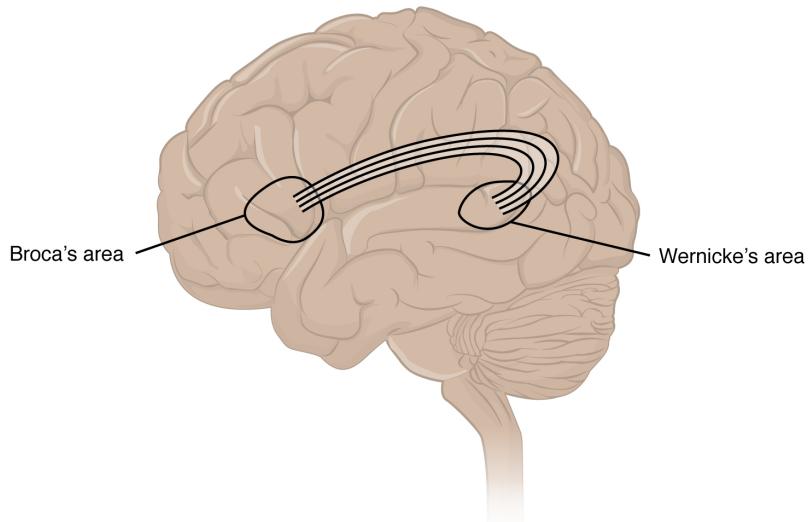
Language is, arguably, a very human aspect of neurological function. There are certainly strides being made in understanding communication in other species, but much of what makes the human experience seemingly unique is its basis in language. Any understanding of our species is necessarily reflective, as suggested by the question “What am I?” And the fundamental answer to this question is suggested by the famous quote by René Descartes: “Cogito Ergo Sum” (translated from Latin as “I think, therefore I am”). Formulating an understanding of yourself is largely describing who you are to yourself. It is a confusing topic to delve into, but language is certainly at the core of what it means to be self-aware.

The neurological exam has two specific subtests that address language. One measures the ability of the patient to understand language by asking them to follow a set of instructions to perform an action, such as “touch your right finger to your left elbow and then to your right knee.” Another subtest assesses the fluency and coherency of language by having the patient generate descriptions of objects or scenes depicted in drawings, and by reciting sentences or explaining a written passage. Language, however, is important in so many ways in the neurological exam. The patient needs to know what to do, whether it is as simple as explaining how the knee-jerk reflex is going

to be performed, or asking a question such as “What is your name?” Often, language deficits can be determined without specific subtests; if a person cannot reply to a question properly, there may be a problem with the reception of language.

An important example of multimodal integrative areas is associated with language function ([Figure 16.6](#)). Adjacent to the auditory association cortex, at the end of the lateral sulcus just anterior to the visual cortex, is **Wernicke's area**. In the lateral aspect of the frontal lobe, just anterior to the region of the motor cortex associated with the head and neck, is Broca's area. Both regions were originally described on the basis of losses of speech and language, which is called **aphasia**. The aphasia associated with Broca's area is known as an **expressive aphasia**, which means that speech production is compromised. This type of aphasia is often described as non-fluency because the ability to say some words leads to broken or halting speech. Grammar can also appear to be lost. The aphasia associated with Wernicke's area is known as a **receptive aphasia**, which is not a loss of speech production, but a loss of understanding of content. Patients, after recovering from acute forms of this aphasia, report not being able to understand what is said to them or what they are saying themselves, but they often cannot keep from talking.

The two regions are connected by white matter tracts that run between the posterior temporal lobe and the lateral aspect of the frontal lobe. **Conduction aphasia** associated with damage to this connection refers to the problem of connecting the understanding of language to the production of speech. This is a very rare condition, but is likely to present as an inability to faithfully repeat spoken language.



**FIGURE 16.6 Broca's and Wernicke's Areas** Two important integration areas of the cerebral cortex associated with language function are Broca's and Wernicke's areas. The two areas are connected through the deep white matter running from the posterior temporal lobe to the frontal lobe.

### Sensorium

Those parts of the brain involved in the reception and interpretation of sensory stimuli are referred to collectively as the sensorium. The cerebral cortex has several regions that are necessary for sensory perception. From the primary cortical areas of the somatosensory, visual, auditory, and gustatory senses to the association areas that process information in these modalities, the cerebral cortex is the seat of conscious sensory perception. In contrast, sensory information can also be processed by deeper brain regions, which we may vaguely describe as subconscious—for instance, we are not constantly aware of the proprioceptive information that the cerebellum uses to maintain balance. Several of the subtests can reveal activity associated with these sensory modalities, such as being able to hear a question or see a picture. Two subtests assess specific functions of these cortical areas.

The first is **praxis**, a practical exercise in which the patient performs a task completely on the basis of verbal description without any demonstration from the examiner. For example, the patient can be told to take their left hand and place it palm down on their left thigh, then flip it over so the palm is facing up, and then repeat this four times. The examiner describes the activity without any movements on their part to suggest how the movements are to be performed. The patient needs to understand the instructions, transform them into movements, and use sensory feedback, both visual and proprioceptive, to perform the movements correctly.

The second subtest for sensory perception is **gnosis**, which involves two tasks. The first task, known as **stereognosis**, involves the naming of objects strictly on the basis of the somatosensory information that comes from manipulating them. The patient keeps their eyes closed and is given a common object, such as a coin, that they have to identify. The patient should be able to indicate the particular type of coin, such as a dime versus a penny, or a nickel versus a quarter, on the basis of the sensory cues involved. For example, the size, thickness, or weight of the coin may be an indication, or to differentiate the pairs of coins suggested here, the smooth or corrugated edge of the coin will correspond to the particular denomination. The second task, **graphesthesia**, is to recognize numbers or letters written on the palm of the hand with a dull pointer, such as a pen cap.

Praxis and gnosis are related to the conscious perception and cortical processing of sensory information. Being able to transform verbal commands into a sequence of motor responses, or to manipulate and recognize a common object and associate it with a name for that object. Both subtests have language components because language function is integral to these functions. The relationship between the words that describe actions, or the nouns that represent objects, and the cerebral location of these concepts is suggested to be localized to particular cortical areas. Certain aphasias can be characterized by a deficit of verbs or nouns, known as V impairment or N impairment, or may be classified as V–N dissociation. Patients have difficulty using one type of word over the other. To describe what is happening in a photograph as part of the expressive language subtest, a patient will use active- or image-based language. The lack of one or the other of these components of language can relate to the ability to use verbs or nouns. Damage to the region at which the frontal and temporal lobes meet, including the region known as the insula, is associated with V impairment; damage to the middle and inferior temporal lobe is associated with N impairment.

### Judgment and Abstract Reasoning

Planning and producing responses requires an ability to make sense of the world around us. Making judgments and reasoning in the abstract are necessary to produce movements as part of larger responses. For example, when your alarm goes off, do you hit the snooze button or jump out of bed? Is 10 extra minutes in bed worth the extra rush to get ready for your day? Will hitting the snooze button multiple times lead to feeling more rested or result in a panic as you run late? How you mentally process these questions can affect your whole day.

The prefrontal cortex is responsible for the functions responsible for planning and making decisions. In the mental status exam, the subtest that assesses judgment and reasoning is directed at three aspects of frontal lobe function. First, the examiner asks questions about problem solving, such as “If you see a house on fire, what would you do?” The patient is also asked to interpret common proverbs, such as “Don’t look a gift horse in the mouth.” Additionally, pairs of words are compared for similarities, such as apple and orange, or lamp and cabinet.

The prefrontal cortex is composed of the regions of the frontal lobe that are not directly related to specific motor functions. The most posterior region of the frontal lobe, the precentral gyrus, is the primary motor cortex. Anterior to that are the premotor cortex, Broca’s area, and the frontal eye fields, which are all related to planning certain types of movements. Anterior to what could be described as motor association areas are the regions of the prefrontal cortex. They are the regions in which judgment, abstract reasoning, and working memory are localized. The antecedents to planning certain movements are judging whether those movements should be made, as in the example of deciding whether to hit the snooze button.

To an extent, the prefrontal cortex may be related to personality. The neurological exam does not necessarily assess personality, but it can be within the realm of neurology or psychiatry. A clinical situation that suggests this link between the prefrontal cortex and personality comes from the story of Phineas Gage, the railroad worker from the mid-1800s who had a metal spike impale his prefrontal cortex. There are suggestions that the steel rod led to changes in his personality. A man who was a quiet, dependable railroad worker became a raucous, irritable drunkard. Later anecdotal evidence from his life suggests that he was able to support himself, although he had to relocate and take on a different career as a stagecoach driver.

A psychiatric practice to deal with various disorders was the prefrontal lobotomy. This procedure was common in the 1940s and early 1950s, until antipsychotic drugs became available. The connections between the prefrontal cortex and other regions of the brain were severed. The disorders associated with this procedure included some aspects of what are now referred to as personality disorders, but also included mood disorders and psychoses. Depictions of lobotomies in popular media suggest a link between cutting the white matter of the prefrontal cortex

and changes in a patient's mood and personality, though this correlation is not well understood.

### Everyday Connection

#### Left Brain, Right Brain

Popular media often refer to right-brained and left-brained people, as if the brain were two independent halves that work differently for different people. This is a popular misinterpretation of an important neurological phenomenon. As an extreme measure to deal with a debilitating condition, the corpus callosum may be sectioned to overcome intractable epilepsy. When the connections between the two cerebral hemispheres are cut, interesting effects can be observed.

If a person with an intact corpus callosum is asked to put their hands in their pockets and describe what is there on the basis of what their hands feel, they might say that they have keys in their right pocket and loose change in the left. They may even be able to count the coins in their pocket and say if they can afford to buy a candy bar from the vending machine. If a person with a sectioned corpus callosum is given the same instructions, they will do something quite peculiar. They will only put their right hand in their pocket and say they have keys there. They will not even move their left hand, much less report that there is loose change in the left pocket.

The reason for this is that the language functions of the cerebral cortex are localized to the left hemisphere in 95 percent of the population. Additionally, the left hemisphere is connected to the right side of the body through the corticospinal tract and the ascending tracts of the spinal cord. Motor commands from the precentral gyrus control the opposite side of the body, whereas sensory information processed by the postcentral gyrus is received from the opposite side of the body. For a verbal command to initiate movement of the right arm and hand, the left side of the brain needs to be connected by the corpus callosum. Language is processed in the left side of the brain and directly influences the left brain and right arm motor functions, but is sent to influence the right brain and left arm motor functions through the corpus callosum. Likewise, the left-handed sensory perception of what is in the left pocket travels across the corpus callosum from the right brain, so no verbal report on those contents would be possible if the hand happened to be in the pocket.

### INTERACTIVE LINK

Watch the [video \(<http://openstax.org/l/2brains>\)](http://openstax.org/l/2brains) titled “The Man With Two Brains” to see the neuroscientist Michael Gazzaniga introduce a patient he has worked with for years who has had his corpus callosum cut, separating his two cerebral hemispheres. A few tests are run to demonstrate how this manifests in tests of cerebral function. Unlike normal people, this patient can perform two independent tasks at the same time because the lines of communication between the right and left sides of his brain have been removed. Whereas a person with an intact corpus callosum cannot overcome the dominance of one hemisphere over the other, this patient can. If the left cerebral hemisphere is dominant in the majority of people, why would right-handedness be most common?

## 16.3 The Cranial Nerve Exam

### LEARNING OBJECTIVES

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

- Describe the functional grouping of cranial nerves
- Match the regions of the forebrain and brain stem that are connected to each cranial nerve
- Suggest diagnoses that would explain certain losses of function in the cranial nerves
- Relate cranial nerve deficits to damage of adjacent, unrelated structures

The twelve cranial nerves are typically covered in introductory anatomy courses, and memorizing their names is facilitated by numerous mnemonics developed by students over the years of this practice. But knowing the names of the nerves in order often leaves much to be desired in understanding what the nerves do. The nerves can be categorized by functions, and subtests of the cranial nerve exam can clarify these functional groupings.

Three of the nerves are strictly responsible for special senses whereas four others contain fibers for special and general senses. Three nerves are connected to the extraocular muscles resulting in the control of gaze. Four nerves

connect to muscles of the face, oral cavity, and pharynx, controlling facial expressions, mastication, swallowing, and speech. Four nerves make up the cranial component of the parasympathetic nervous system responsible for pupillary constriction, salivation, and the regulation of the organs of the thoracic and upper abdominal cavities. Finally, one nerve controls the muscles of the neck, assisting with spinal control of the movement of the head and neck.

The cranial nerve exam allows directed tests of forebrain and brain stem structures. The twelve cranial nerves serve the head and neck. The vagus nerve (cranial nerve X) has autonomic functions in the thoracic and superior abdominal cavities. The special senses are served through the cranial nerves, as well as the general senses of the head and neck. The movement of the eyes, face, tongue, throat, and neck are all under the control of cranial nerves. Preganglionic parasympathetic nerve fibers that control pupillary size, salivary glands, and the thoracic and upper abdominal viscera are found in four of the nerves. Tests of these functions can provide insight into damage to specific regions of the brain stem and may uncover deficits in adjacent regions.

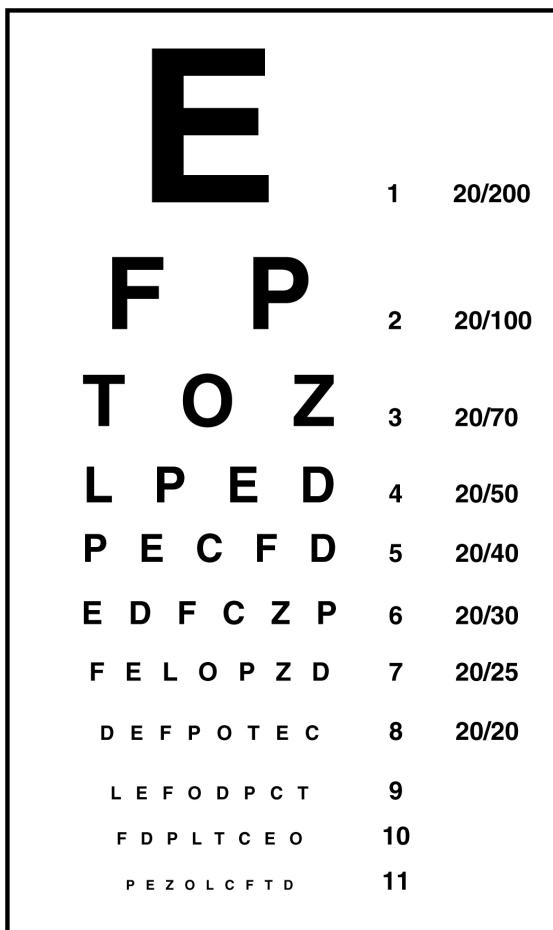
### Sensory Nerves

The olfactory, optic, and vestibulocochlear nerves (cranial nerves I, II, and VIII) are dedicated to four of the special senses: smell, vision, equilibrium, and hearing, respectively. Taste sensation is relayed to the brain stem through fibers of the facial and glossopharyngeal nerves. The trigeminal nerve is a mixed nerve that carries the general somatic senses from the head, similar to those coming through spinal nerves from the rest of the body.

Testing smell is straightforward, as common smells are presented to one nostril at a time. The patient should be able to recognize the smell of coffee or mint, indicating the proper functioning of the olfactory system. Loss of the sense of smell is called anosmia and can be lost following blunt trauma to the head or through aging. The short axons of the first cranial nerve regenerate on a regular basis. The neurons in the olfactory epithelium have a limited life span, and new cells grow to replace the ones that die off. The axons from these neurons grow back into the CNS by following the existing axons—representing one of the few examples of such growth in the mature nervous system. If all of the fibers are sheared when the brain moves within the cranium, such as in a motor vehicle accident, then no axons can find their way back to the olfactory bulb to re-establish connections. If the nerve is not completely severed, the anosmia may be temporary as new neurons can eventually reconnect.

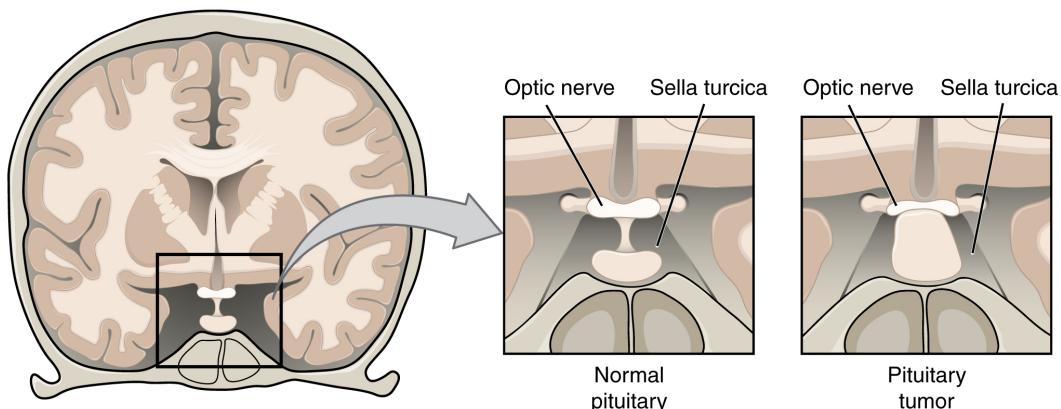
Olfaction is not the pre-eminent sense, but its loss can be quite detrimental. The enjoyment of food is largely based on our sense of smell. Anosmia means that food will not seem to have the same taste, though the gustatory sense is intact, and food will often be described as being bland. However, the taste of food can be improved by adding ingredients (e.g., salt) that stimulate the gustatory sense.

Testing vision relies on the tests that are common in an optometry office. The **Snellen chart** ([Figure 16.7](#)) demonstrates visual acuity by presenting standard Roman letters in a variety of sizes. The result of this test is a rough generalization of the acuity of a person based on the normal accepted acuity, such that a letter that subtends a visual angle of 5 minutes of an arc at 20 feet can be seen. To have 20/60 vision, for example, means that the smallest letters that a person can see at a 20-foot distance could be seen by a person with normal acuity from 60 feet away. Testing the extent of the visual field means that the examiner can establish the boundaries of peripheral vision as simply as holding their hands out to either side and asking the patient when the fingers are no longer visible without moving the eyes to track them. If it is necessary, further tests can establish the perceptions in the visual fields. Physical inspection of the optic disk, or where the optic nerve emerges from the eye, can be accomplished by looking through the pupil with an ophthalmoscope.



**FIGURE 16.7 The Snellen Chart** The Snellen chart for visual acuity presents a limited number of Roman letters in lines of decreasing size. The line with letters that subtend 5 minutes of an arc from 20 feet represents the smallest letters that a person with normal acuity should be able to read at that distance. The different sizes of letters in the other lines represent rough approximations of what a person of normal acuity can read at different distances. For example, the line that represents 20/200 vision would have larger letters so that they are legible to the person with normal acuity at 200 feet.

The optic nerves from both sides enter the cranium through the respective optic canals and meet at the optic chiasm at which fibers sort such that the two halves of the visual field are processed by the opposite sides of the brain. Deficits in visual field perception often suggest damage along the length of the optic pathway between the orbit and the diencephalon. For example, loss of peripheral vision may be the result of a pituitary tumor pressing on the optic chiasm (Figure 16.8). The pituitary, seated in the sella turcica of the sphenoid bone, is directly inferior to the optic chiasm. The axons that decussate in the chiasm are from the medial retinæ of either eye, and therefore carry information from the peripheral visual field.



**FIGURE 16.8 Pituitary Tumor** The pituitary gland is located in the sella turcica of the sphenoid bone within the cranial floor, placing it immediately inferior to the optic chiasm. If the pituitary gland develops a tumor, it can press against the fibers crossing in the chiasm.

Those fibers are conveying peripheral visual information to the opposite side of the brain, so the patient will experience “tunnel vision”—meaning that only the central visual field will be perceived.

The vestibulocochlear nerve (CN VIII) carries both equilibrium and auditory sensations from the inner ear to the medulla. Though the two senses are not directly related, anatomy is mirrored in the two systems. Problems with balance, such as vertigo, and deficits in hearing may both point to problems with the inner ear. Within the petrous region of the temporal bone is the bony labyrinth of the inner ear. The vestibule is the portion for equilibrium, composed of the utricle, saccule, and the three semicircular canals. The cochlea is responsible for transducing sound waves into a neural signal. The sensory nerves from these two structures travel side-by-side as the vestibulocochlear nerve, though they are really separate divisions. They both emerge from the inner ear, pass through the internal auditory meatus, and synapse in nuclei of the superior medulla. Though they are part of distinct sensory systems, the vestibular nuclei and the cochlear nuclei are close neighbors with adjacent inputs. Deficits in one or both systems could occur from damage that encompasses structures close to both. Damage to structures near the two nuclei can result in deficits to one or both systems.

Balance or hearing deficits may be the result of damage to the middle or inner ear structures. Ménière's disease is a disorder that can affect both equilibrium and audition in a variety of ways. The patient can suffer from vertigo, a low-frequency ringing in the ears, or a loss of hearing. From patient to patient, the exact presentation of the disease can be different. Additionally, within a single patient, the symptoms and signs may change as the disease progresses. Use of the neurological exam subtests for the vestibulocochlear nerve illuminates the changes a patient may go through. The disease appears to be the result of accumulation, or over-production, of fluid in the inner ear, in either the vestibule or cochlea.

Tests of equilibrium are important for coordination and gait and are related to other aspects of the neurological exam. The vestibulo-ocular reflex involves the cranial nerves for gaze control. Balance and equilibrium, as tested by the Romberg test, are part of spinal and cerebellar processes and involved in those components of the neurological exam, as discussed later.

Hearing is tested by using a tuning fork in a couple of different ways. The **Rinne test** involves using a tuning fork to distinguish between **conductive hearing** and **sensorineural hearing**. Conductive hearing relies on vibrations being conducted through the ossicles of the middle ear. Sensorineural hearing is the transmission of sound stimuli through the neural components of the inner ear and cranial nerve. A vibrating tuning fork is placed on the mastoid process and the patient indicates when the sound produced from this is no longer present. Then the fork is immediately moved to just next to the ear canal so the sound travels through the air. If the sound is not heard through the ear, meaning the sound is conducted better through the temporal bone than through the ossicles, a conductive hearing deficit is present. The **Weber test** also uses a tuning fork to differentiate between conductive versus sensorineural hearing loss. In this test, the tuning fork is placed at the top of the skull, and the sound of the tuning fork reaches both inner ears by travelling through bone. In a healthy patient, the sound would appear equally loud in both ears. With unilateral conductive hearing loss, however, the tuning fork sounds louder in the ear with hearing loss. This is because the sound of the tuning fork has to compete with background noise coming from the outer ear, but in conductive hearing loss, the background noise is blocked in the damaged ear, allowing the tuning fork to sound relatively louder in that ear. With unilateral sensorineural hearing loss, however, damage to the cochlea or associated nervous tissue means that the tuning fork sounds quieter in that ear.

The trigeminal system of the head and neck is the equivalent of the ascending spinal cord systems of the dorsal column and the spinothalamic pathways. Somatosensation of the face is conveyed along the nerve to enter the brain stem at the level of the pons. Synapses of those axons, however, are distributed across nuclei found throughout the brain stem. The mesencephalic nucleus processes proprioceptive information of the face, which is the movement and position of facial muscles. It is the sensory component of the **jaw-jerk reflex**, a stretch reflex of the masseter muscle. The chief nucleus, located in the pons, receives information about light touch as well as proprioceptive information about the mandible, which are both relayed to the thalamus and, ultimately, to the postcentral gyrus of the parietal lobe. The spinal trigeminal nucleus, located in the medulla, receives information about crude touch, pain, and temperature to be relayed to the thalamus and cortex. Essentially, the projection through the chief nucleus is analogous to the dorsal column pathway for the body, and the projection through the spinal trigeminal nucleus is analogous to the spinothalamic pathway.

Subtests for the sensory component of the trigeminal system are the same as those for the sensory exam targeting

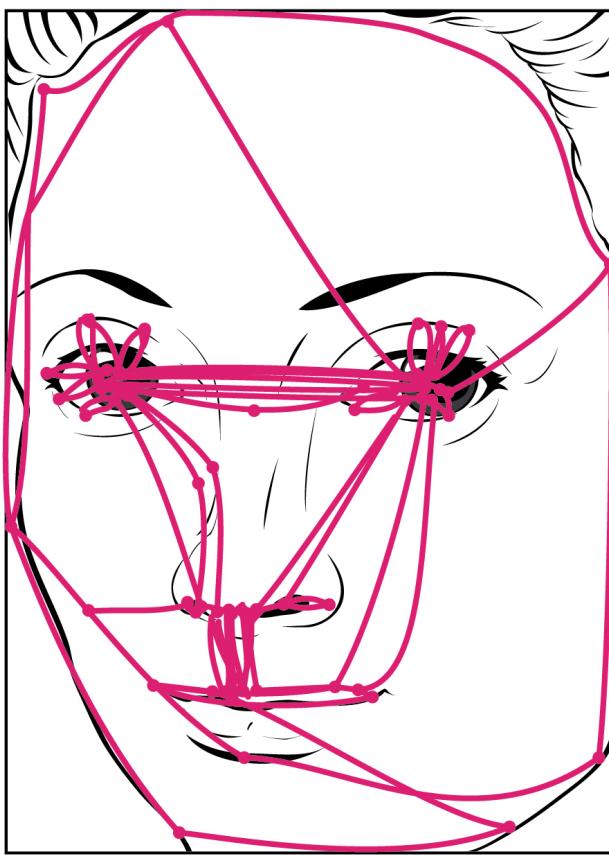
the spinal nerves. The primary sensory subtest for the trigeminal system is sensory discrimination. A cotton-tipped applicator, which is cotton attached to the end of a thin wooden stick, can be used easily for this. The wood of the applicator can be snapped so that a pointed end is opposite the soft cotton-tipped end. The cotton end provides a touch stimulus, while the pointed end provides a painful, or sharp, stimulus. While the patient's eyes are closed, the examiner touches the two ends of the applicator to the patient's face, alternating randomly between them. The patient must identify whether the stimulus is sharp or dull. These stimuli are processed by the trigeminal system separately. Contact with the cotton tip of the applicator is a light touch, relayed by the chief nucleus, but contact with the pointed end of the applicator is a painful stimulus relayed by the spinal trigeminal nucleus. Failure to discriminate these stimuli can localize problems within the brain stem. If a patient cannot recognize a painful stimulus, that might indicate damage to the spinal trigeminal nucleus in the medulla. The medulla also contains important regions that regulate the cardiovascular, respiratory, and digestive systems, as well as being the pathway for ascending and descending tracts between the brain and spinal cord. Damage, such as a stroke, that results in changes in sensory discrimination may indicate these unrelated regions are affected as well.

### Gaze Control

The three nerves that control the extraocular muscles are the oculomotor, trochlear, and abducens nerves, which are the third, fourth, and sixth cranial nerves. As the name suggests, the abducens nerve is responsible for abducting the eye, which it controls through contraction of the lateral rectus muscle. The trochlear nerve controls the superior oblique muscle to rotate the eye along its axis in the orbit medially, which is called **intorsion**, and is a component of focusing the eyes on an object close to the face. The oculomotor nerve controls all the other extraocular muscles, as well as a muscle of the upper eyelid. Movements of the two eyes need to be coordinated to locate and track visual stimuli accurately. When moving the eyes to locate an object in the horizontal plane, or to track movement horizontally in the visual field, the lateral rectus muscle of one eye and medial rectus muscle of the other eye are both active. The lateral rectus is controlled by neurons of the abducens nucleus in the superior medulla, whereas the medial rectus is controlled by neurons in the oculomotor nucleus of the midbrain.

Coordinated movement of both eyes through different nuclei requires integrated processing through the brain stem. In the midbrain, the superior colliculus integrates visual stimuli with motor responses to initiate eye movements. The **paramedian pontine reticular formation (PPRF)** will initiate a rapid eye movement, or **saccade**, to bring the eyes to bear on a visual stimulus quickly. These areas are connected to the oculomotor, trochlear, and abducens nuclei by the **medial longitudinal fasciculus (MLF)** that runs through the majority of the brain stem. The MLF allows for **conjugate gaze**, or the movement of the eyes in the same direction, during horizontal movements that require the lateral and medial rectus muscles. Control of conjugate gaze strictly in the vertical direction is contained within the oculomotor complex. To elevate the eyes, the oculomotor nerve on either side stimulates the contraction of both superior rectus muscles; to depress the eyes, the oculomotor nerve on either side stimulates the contraction of both inferior rectus muscles.

Purely vertical movements of the eyes are not very common. Movements are often at an angle, so some horizontal components are necessary, adding the medial and lateral rectus muscles to the movement. The rapid movement of the eyes used to locate and direct the fovea onto visual stimuli is called a saccade. Notice that the paths that are traced in [Figure 16.9](#) are not strictly vertical. The movements between the nose and the mouth are closest, but still have a slant to them. Also, the superior and inferior rectus muscles are not perfectly oriented with the line of sight. The origin for both muscles is medial to their insertions, so elevation and depression may require the lateral rectus muscles to compensate for the slight adduction inherent in the contraction of those muscles, requiring MLF activity as well.



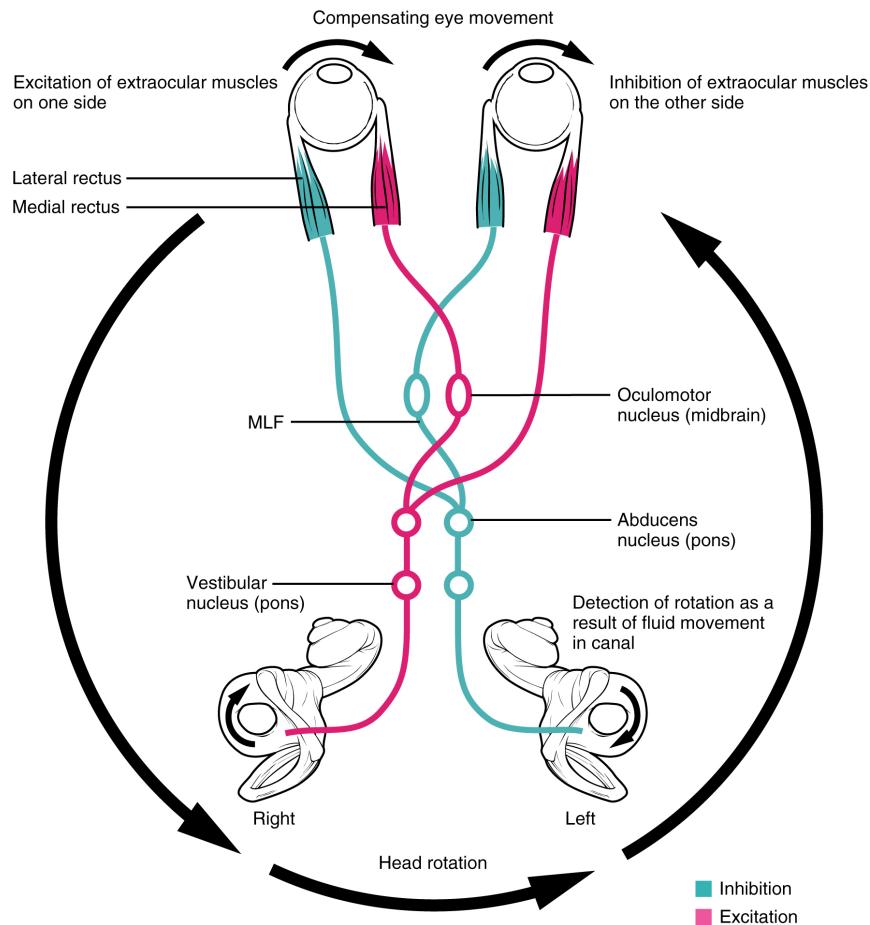
**FIGURE 16.9 Saccadic Eye Movements** Saccades are rapid, conjugate movements of the eyes to survey a complicated visual stimulus, or to follow a moving visual stimulus. This image represents the shifts in gaze typical of a person studying a face. Notice the concentration of gaze on the major features of the face and the large number of paths traced between the eyes or around the mouth.

Testing eye movement is simply a matter of having the patient track the tip of a pen as it is passed through the visual field. This may appear similar to testing visual field deficits related to the optic nerve, but the difference is that the patient is asked to not move the eyes while the examiner moves a stimulus into the peripheral visual field. Here, the extent of movement is the point of the test. The examiner is watching for conjugate movements representing proper function of the related nuclei and the MLF. Failure of one eye to abduct while the other adducts in a horizontal movement is referred to as **internuclear ophthalmoplegia**. When this occurs, the patient will experience **diplopia**, or double vision, as the two eyes are temporarily pointed at different stimuli. Diplopia is not restricted to failure of the lateral rectus, because any of the extraocular muscles may fail to move one eye in perfect conjugation with the other.

The final aspect of testing eye movements is to move the tip of the pen in toward the patient's face. As visual stimuli move closer to the face, the two medial recti muscles cause the eyes to move in the one nonconjugate movement that is part of gaze control. When the two eyes move to look at something closer to the face, they both adduct, which is referred to as **convergence**. To keep the stimulus in focus, the eye also needs to change the shape of the lens, which is controlled through the parasympathetic fibers of the oculomotor nerve. The change in focal power of the eye is referred to as **accommodation**. Accommodation ability changes with age; focusing on nearer objects, such as the written text of a book or on a computer screen, may require corrective lenses later in life. Coordination of the skeletal muscles for convergence and coordination of the smooth muscles of the ciliary body for accommodation are referred to as the **accommodation-convergence reflex**.

A crucial function of the cranial nerves is to keep visual stimuli centered on the fovea of the retina. The **vestibulo-ocular reflex (VOR)** coordinates all of the components (Figure 16.10), both sensory and motor, that make this possible. If the head rotates in one direction—for example, to the right—the horizontal pair of semicircular canals in the inner ear indicate the movement by increased activity on the right and decreased activity on the left. The information is sent to the abducens nuclei and oculomotor nuclei on either side to coordinate the lateral and medial rectus muscles. The left lateral rectus and right medial rectus muscles will contract, rotating the eyes in the

opposite direction of the head, while nuclei controlling the right lateral rectus and left medial rectus muscles will be inhibited to reduce antagonism of the contracting muscles. These actions stabilize the visual field by compensating for the head rotation with opposite rotation of the eyes in the orbits. Deficits in the VOR may be related to vestibular damage, such as in Ménière's disease, or from dorsal brain stem damage that would affect the eye movement nuclei or their connections through the MLF.



**FIGURE 16.10 Vestibulo-ocular Reflex** If the head is turned in one direction, the coordination of that movement with the fixation of the eyes on a visual stimulus involves a circuit that ties the vestibular sense with the eye movement nuclei through the MLF.

### Nerves of the Face and Oral Cavity

An iconic part of a doctor's visit is the inspection of the oral cavity and pharynx, suggested by the directive to "open your mouth and say 'ah.'" This is followed by inspection, with the aid of a tongue depressor, of the back of the mouth, or the opening of the oral cavity into the pharynx known as the **fauces**. Whereas this portion of a medical exam inspects for signs of infection, such as in tonsillitis, it is also the means to test the functions of the cranial nerves that are associated with the oral cavity.

The facial and glossopharyngeal nerves convey gustatory stimulation to the brain. Testing this is as simple as introducing salty, sour, bitter, or sweet stimuli to either side of the tongue. The patient should respond to the taste stimulus before retracting the tongue into the mouth. Stimuli applied to specific locations on the tongue will dissolve into the saliva and may stimulate taste buds connected to either the left or right of the nerves, masking any lateral deficits. Along with taste, the glossopharyngeal nerve relays general sensations from the pharyngeal walls. These sensations, along with certain taste stimuli, can stimulate the gag reflex. If the examiner moves the tongue depressor to contact the lateral wall of the fauces, this should elicit the gag reflex. Stimulation of either side of the fauces should elicit an equivalent response. The motor response, through contraction of the muscles of the pharynx, is mediated through the vagus nerve. Normally, the vagus nerve is considered autonomic in nature. The vagus nerve directly stimulates the contraction of skeletal muscles in the pharynx and larynx to contribute to the swallowing and speech functions. Further testing of vagus motor function has the patient repeating consonant sounds that require

movement of the muscles around the fauces. The patient is asked to say “lah-kah-pah” or a similar set of alternating sounds while the examiner observes the movements of the soft palate and arches between the palate and tongue.

The facial and glossopharyngeal nerves are also responsible for the initiation of salivation. Neurons in the salivary nuclei of the medulla project through these two nerves as preganglionic fibers, and synapse in ganglia located in the head. The parasympathetic fibers of the facial nerve synapse in the pterygopalatine ganglion, which projects to the submandibular gland and sublingual gland. The parasympathetic fibers of the glossopharyngeal nerve synapse in the otic ganglion, which projects to the parotid gland. Salivation in response to food in the oral cavity is based on a visceral reflex arc within the facial or glossopharyngeal nerves. Other stimuli that stimulate salivation are coordinated through the hypothalamus, such as the smell and sight of food.

The hypoglossal nerve is the motor nerve that controls the muscles of the tongue, except for the palatoglossus muscle, which is controlled by the vagus nerve. There are two sets of muscles of the tongue. The **extrinsic muscles of the tongue** are connected to other structures, whereas the **intrinsic muscles of the tongue** are completely contained within the lingual tissues. While examining the oral cavity, movement of the tongue will indicate whether hypoglossal function is impaired. The test for hypoglossal function is the “stick out your tongue” part of the exam. The genioglossus muscle is responsible for protrusion of the tongue. If the hypoglossal nerves on both sides are working properly, then the tongue will stick straight out. If the nerve on one side has a deficit, the tongue will stick out to that side—pointing to the side with damage. Loss of function of the tongue can interfere with speech and swallowing. Additionally, because the location of the hypoglossal nerve and nucleus is near the cardiovascular center, inspiratory and expiratory areas for respiration, and the vagus nuclei that regulate digestive functions, a tongue that protrudes incorrectly can suggest damage in adjacent structures that have nothing to do with controlling the tongue.

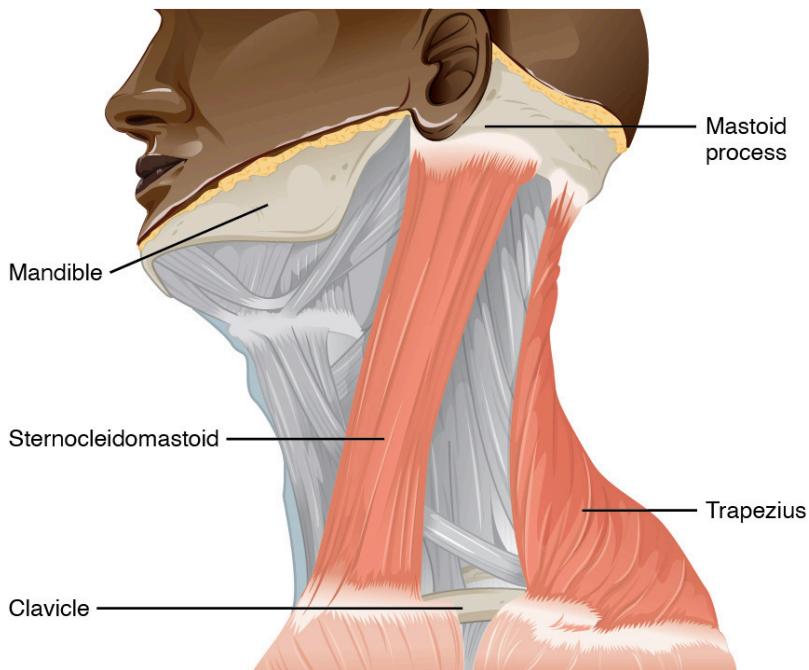
### **INTERACTIVE LINK**

Watch this short [video \(<http://openstax.org/l/facialnerve>\)](http://openstax.org/l/facialnerve) to see an examination of the facial nerve using some simple tests. The facial nerve controls the muscles of facial expression. Severe deficits will be obvious in watching someone use those muscles for normal control. One side of the face might not move like the other side. But directed tests, especially for contraction against resistance, require a formal testing of the muscles. The muscles of the upper and lower face need to be tested. The strength test in this video involves the patient squeezing her eyes shut and the examiner trying to pry her eyes open. Why does the examiner ask her to try a second time?

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### **Motor Nerves of the Neck**

The accessory nerve, also referred to as the spinal accessory nerve, innervates the sternocleidomastoid and trapezius muscles ([Figure 16.11](#)). When both the sternocleidomastoids contract, the head flexes forward; individually, they cause rotation to the opposite side. The trapezius can act as an antagonist, causing extension and hyperextension of the neck. These two superficial muscles are important for changing the position of the head. Both muscles also receive input from cervical spinal nerves. Along with the spinal accessory nerve, these nerves contribute to elevating the scapula and clavicle through the trapezius, which is tested by asking the patient to shrug both shoulders, and watching for asymmetry. For the sternocleidomastoid, those spinal nerves are primarily sensory projections, whereas the trapezius also has lateral insertions to the clavicle and scapula, and receives motor input from the spinal cord. Calling the nerve the spinal accessory nerve suggests that it is aiding the spinal nerves. Though that is not precisely how the name originated, it does help make the association between the function of this nerve in controlling these muscles and the role these muscles play in movements of the trunk or shoulders.



**FIGURE 16.11 Muscles Controlled by the Accessory Nerve** The accessory nerve innervates the sternocleidomastoid and trapezius muscles, both of which attach to the head and to the trunk and shoulders. They can act as antagonists in head flexion and extension, and as synergists in lateral flexion toward the shoulder.

To test these muscles, the patient is asked to flex and extend the neck or shrug the shoulders against resistance, testing the strength of the muscles. Lateral flexion of the neck toward the shoulder tests both at the same time. Any difference on one side versus the other would suggest damage on the weaker side. These strength tests are common for the skeletal muscles controlled by spinal nerves and are a significant component of the motor exam. Deficits associated with the accessory nerve may have an effect on orienting the head, as described with the VOR.



## HOMEOSTATIC IMBALANCES

### The Pupillary Light Response

The autonomic control of pupillary size in response to a bright light involves the sensory input of the optic nerve and the parasympathetic motor output of the oculomotor nerve. When light hits the retina, specialized photosensitive ganglion cells send a signal along the optic nerve to the pretectal nucleus in the superior midbrain. A neuron from this nucleus projects to the Edinger-Westphal nuclei in the oculomotor complex in both sides of the midbrain. Neurons in this nucleus give rise to the preganglionic parasympathetic fibers that project through the oculomotor nerve to the ciliary ganglion in the posterior orbit. The postganglionic parasympathetic fibers from the ganglion project to the iris, where they release acetylcholine onto circular fibers that constrict the pupil to reduce the amount of light hitting the retina. The sympathetic nervous system is responsible for dilating the pupil when light levels are low.

Shining light in one eye will elicit constriction of both pupils. The efferent limb of the pupillary light reflex is bilateral. Light shined in one eye causes a constriction of that pupil, as well as constriction of the contralateral pupil. Shining a penlight in the eye of a patient is a very artificial situation, as both eyes are normally exposed to the same light sources. Testing this reflex can illustrate whether the optic nerve or the oculomotor nerve is damaged. If shining the light in one eye results in no changes in pupillary size but shining light in the opposite eye elicits a normal, bilateral response, the damage is associated with the optic nerve on the nonresponsive side. If light in either eye elicits a response in only one eye, the problem is with the oculomotor system.

If light in the right eye only causes the left pupil to constrict, the direct reflex is lost and the consensual reflex is intact, which means that the right oculomotor nerve (or Edinger-Westphal nucleus) is damaged. Damage to the right oculomotor connections will be evident when light is shined in the left eye. In that case, the direct reflex is intact but the consensual reflex is lost, meaning that the left pupil will constrict while the right does not.

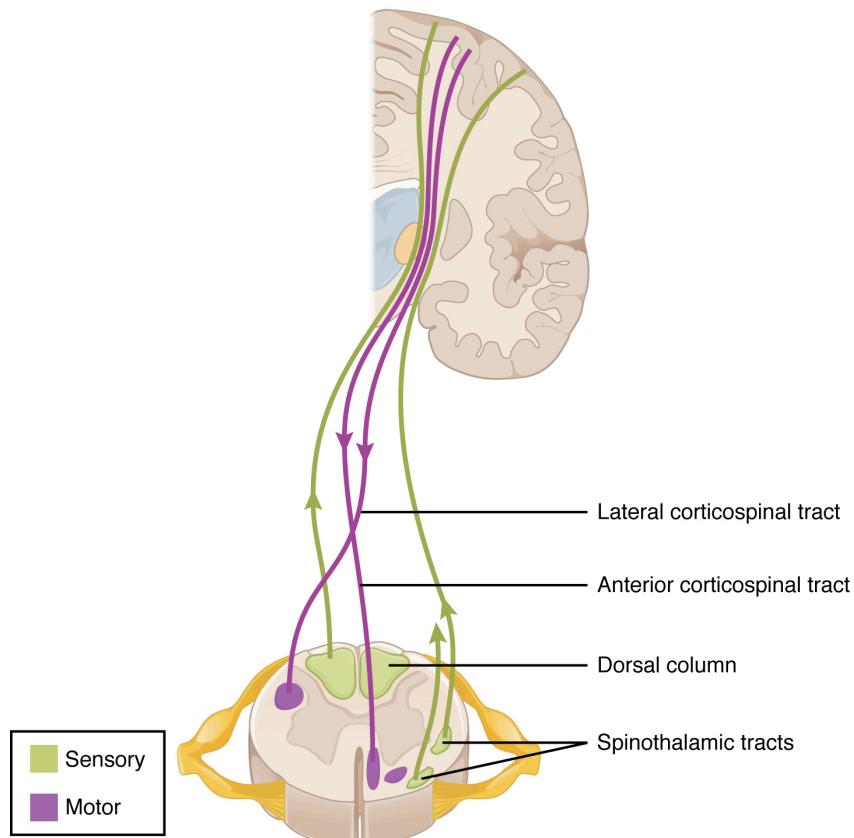
## 16.4 The Sensory and Motor Exams

### LEARNING OBJECTIVES

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

- Describe the arrangement of sensory and motor regions in the spinal cord
- Relate damage in the spinal cord to sensory or motor deficits
- Differentiate between upper motor neuron and lower motor neuron diseases
- Describe the clinical indications of common reflexes

Connections between the body and the CNS occur through the spinal cord. The cranial nerves connect the head and neck directly to the brain, but the spinal cord receives sensory input and sends motor commands out to the body through the spinal nerves. Whereas the brain develops into a complex series of nuclei and fiber tracts, the spinal cord remains relatively simple in its configuration (Figure 16.12). From the initial neural tube early in embryonic development, the spinal cord retains a tube-like structure with gray matter surrounding the small central canal and white matter on the surface in three columns. The dorsal, or posterior, horns of the gray matter are mainly devoted to sensory functions whereas the ventral, or anterior, and lateral horns are associated with motor functions. In the white matter, the dorsal column relays sensory information to the brain, and the anterior column is almost exclusively relaying motor commands to the ventral horn motor neurons. The lateral column, however, conveys both sensory and motor information between the spinal cord and brain.

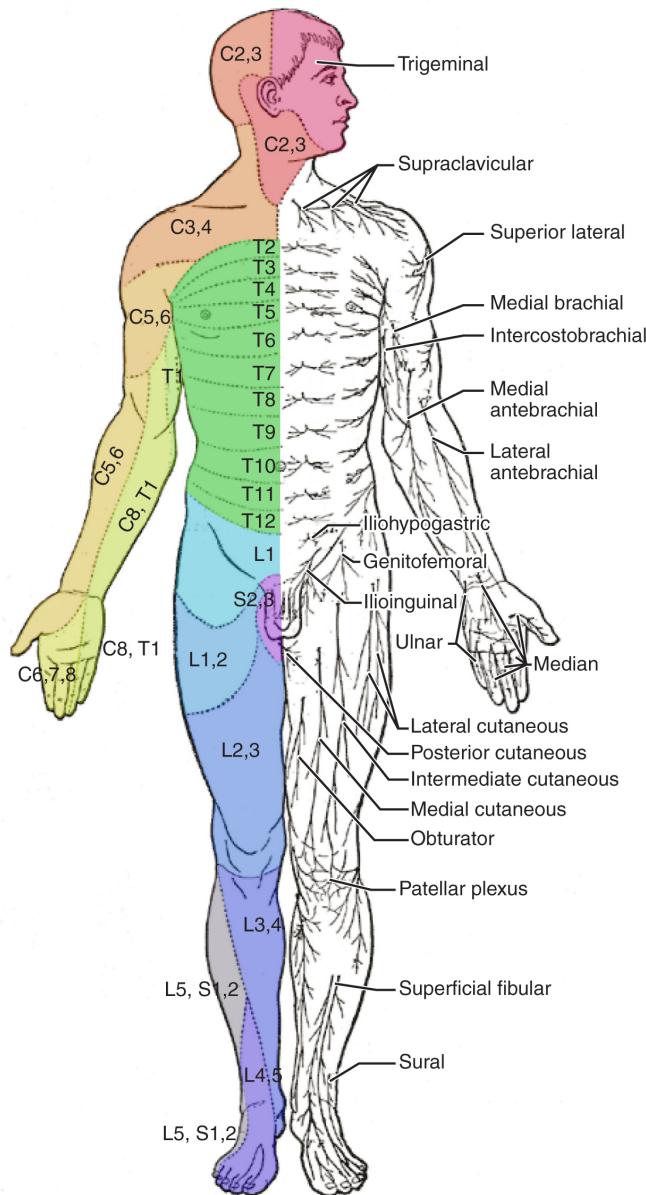


**FIGURE 16.12** Locations of Spinal Fiber Tracts

### Sensory Modalities and Location

The general senses are distributed throughout the body, relying on nervous tissue incorporated into various organs. Somatic senses are incorporated mostly into the skin, muscles, or tendons, whereas the visceral senses come from nervous tissue incorporated into the majority of organs such as the heart or stomach. The somatic senses are those that usually make up the conscious perception of how the body interacts with the environment. The visceral senses are most often below the limit of conscious perception because they are involved in homeostatic regulation through the autonomic nervous system.

The sensory exam tests the somatic senses, meaning those that are consciously perceived. Testing of the senses begins with examining the regions known as dermatomes that connect to the cortical region where somatosensation is perceived in the postcentral gyrus. To test the sensory fields, a simple stimulus of the light touch of the soft end of a cotton-tipped applicator is applied at various locations on the skin. The spinal nerves, which contain sensory fibers with dendritic endings in the skin, connect with the skin in a topographically organized manner, illustrated as dermatomes (Figure 16.13). For example, the fibers of eighth cervical nerve innervate the medial surface of the forearm and extend out to the fingers. In addition to testing perception at different positions on the skin, it is necessary to test sensory perception within the dermatome from distal to proximal locations in the appendages, or lateral to medial locations in the trunk. In testing the eighth cervical nerve, the patient would be asked if the touch of the cotton to the fingers or the medial forearm was perceptible, and whether there were any differences in the sensations.



**FIGURE 16.13 Dermatomes** The surface of the skin can be divided into topographic regions that relate to the location of sensory endings in the skin based on the spinal nerve that contains those fibers. (credit: modification of work by Mikael Häggström)

Other modalities of somatosensation can be tested using a few simple tools. The perception of pain can be tested using the broken end of the cotton-tipped applicator. The perception of vibratory stimuli can be tested using an oscillating tuning fork placed against prominent bone features such as the distal head of the ulna on the medial aspect of the elbow. When the tuning fork is still, the metal against the skin can be perceived as a cold stimulus.

Using the cotton tip of the applicator, or even just a fingertip, the perception of tactile movement can be assessed as the stimulus is drawn across the skin for approximately 2–3 cm. The patient would be asked in what direction the stimulus is moving. All of these tests are repeated in distal and proximal locations and for different dermatomes to assess the spatial specificity of perception. The sense of position and motion, proprioception, is tested by moving the fingers or toes and asking the patient if they sense the movement. If the distal locations are not perceived, the test is repeated at increasingly proximal joints.

The various stimuli used to test sensory input assess the function of the major ascending tracts of the spinal cord. The dorsal column pathway conveys fine touch, vibration, and proprioceptive information, whereas the spinothalamic pathway primarily conveys pain and temperature. Testing these stimuli provides information about whether these two major ascending pathways are functioning properly. Within the spinal cord, the two systems are segregated. The dorsal column information ascends ipsilateral to the source of the stimulus and decussates in the medulla, whereas the spinothalamic pathway decussates at the level of entry and ascends contralaterally. The differing sensory stimuli are segregated in the spinal cord so that the various subtests for these stimuli can distinguish which ascending pathway may be damaged in certain situations.

Whereas the basic sensory stimuli are assessed in the subtests directed at each submodality of somatosensation, testing the ability to discriminate sensations is important. Pairing the light touch and pain subtests together makes it possible to compare the two submodalities at the same time, and therefore the two major ascending tracts at the same time. Mistaking painful stimuli for light touch, or vice versa, may point to errors in ascending projections, such as in a **hemisection** of the spinal cord that might come from a motor vehicle accident.

Another issue of sensory discrimination is not distinguishing between different submodalities, but rather location. The two-point discrimination subtest highlights the density of sensory endings, and therefore receptive fields in the skin. The sensitivity to fine touch, which can give indications of the texture and detailed shape of objects, is highest in the fingertips. To assess the limit of this sensitivity, two-point discrimination is measured by simultaneously touching the skin in two locations, such as could be accomplished with a pair of forceps. Specialized calipers for precisely measuring the distance between points are also available. The patient is asked to indicate whether one or two stimuli are present while keeping their eyes closed. The examiner will switch between using the two points and a single point as the stimulus. Failure to recognize two points may be an indication of a dorsal column pathway deficit.

Similar to two-point discrimination, but assessing laterality of perception, is double simultaneous stimulation. Two stimuli, such as the cotton tips of two applicators, are touched to the same position on both sides of the body. If one side is not perceived, this may indicate damage to the contralateral posterior parietal lobe. Because there is one of each pathway on either side of the spinal cord, they are not likely to interact. If none of the other subtests suggest particular deficits with the pathways, the deficit is likely to be in the cortex where conscious perception is based. The mental status exam contains subtests that assess other functions that are primarily localized to the parietal cortex, such as stereognosis and graphesthesia.

A final subtest of sensory perception that concentrates on the sense of proprioception is known as the **Romberg test**. The patient is asked to stand straight with feet together. Once the patient has achieved their balance in that position, they are asked to close their eyes. Without visual feedback that the body is in a vertical orientation relative to the surrounding environment, the patient must rely on the proprioceptive stimuli of joint and muscle position, as well as information from the inner ear, to maintain balance. This test can indicate deficits in dorsal column pathway proprioception, as well as problems with proprioceptive projections to the cerebellum through the **spinocerebellar tract**.

## INTERACTIVE LINK

Watch this [video](http://openstax.org/l/2point) (<http://openstax.org/l/2point>) to see a quick demonstration of two-point discrimination. Touching a specialized caliper to the surface of the skin will measure the distance between two points that are perceived as distinct stimuli versus a single stimulus. The patient keeps their eyes closed while the examiner switches between using both points of the caliper or just one. The patient then must indicate whether one or two stimuli are in contact with the skin. Why is the distance between the caliper points closer on the fingertips as opposed to the palm of the hand? And what do you think the distance would be on the arm, or the shoulder?

## Muscle Strength and Voluntary Movement

The skeleto-motor system is largely based on the simple, two-cell projection from the precentral gyrus of the frontal lobe to the skeletal muscles. The corticospinal tract represents the neurons that send output from the primary motor cortex. These fibers travel through the deep white matter of the cerebrum, then through the midbrain and pons, into the medulla where most of them decussate, and finally through the spinal cord white matter in the lateral (crossed fibers) or anterior (uncrossed fibers) columns. These fibers synapse on motor neurons in the ventral horn. The ventral horn motor neurons then project to skeletal muscle and cause contraction. These two cells are termed the upper motor neuron (UMN) and the lower motor neuron (LMN). Voluntary movements require these two cells to be active.

The motor exam tests the function of these neurons and the muscles they control. First, the muscles are inspected and palpated for signs of structural irregularities. Movement disorders may be the result of changes to the muscle tissue, such as scarring, and these possibilities need to be ruled out before testing function. Along with this inspection, muscle tone is assessed by moving the muscles through a passive range of motion. The arm is moved at the elbow and wrist, and the leg is moved at the knee and ankle. Skeletal muscle should have a resting tension representing a slight contraction of the fibers. The lack of muscle tone, known as **hypotonicity** or **flaccidity**, may indicate that the LMN is not conducting action potentials that will keep a basal level of acetylcholine in the neuromuscular junction.

If muscle tone is present, muscle strength is tested by having the patient contract muscles against resistance. The examiner will ask the patient to lift the arm, for example, while the examiner is pushing down on it. This is done for both limbs, including shrugging the shoulders. Lateral differences in strength—being able to push against resistance with the right arm but not the left—would indicate a deficit in one corticospinal tract versus the other. An overall loss of strength, without laterality, could indicate a global problem with the motor system. Diseases that result in UMN lesions include cerebral palsy or MS, or it may be the result of a stroke. A sign of UMN lesion is a negative result in the subtest for **pronator drift**. The patient is asked to extend both arms in front of the body with the palms facing up. While keeping the eyes closed, if the patient unconsciously allows one or the other arm to slowly relax, toward the pronated position, this could indicate a failure of the motor system to maintain the supinated position.

## Reflexes

Reflexes combine the spinal sensory and motor components with a sensory input that directly generates a motor response. The reflexes that are tested in the neurological exam are classified into two groups. A **deep tendon reflex** is commonly known as a stretch reflex, and is elicited by a strong tap to a tendon, such as in the knee-jerk reflex. A **superficial reflex** is elicited through gentle stimulation of the skin and causes contraction of the associated muscles.

For the arm, the common reflexes to test are of the biceps, brachioradialis, triceps, and flexors for the digits. For the leg, the knee-jerk reflex of the quadriceps is common, as is the ankle reflex for the gastrocnemius and soleus. The tendon at the insertion for each of these muscles is struck with a rubber mallet. The muscle is quickly stretched, resulting in activation of the muscle spindle that sends a signal into the spinal cord through the dorsal root. The fiber synapses directly on the ventral horn motor neuron that activates the muscle, causing contraction. The reflexes are physiologically useful for stability. If a muscle is stretched, it reflexively contracts to return the muscle to compensate for the change in length. In the context of the neurological exam, reflexes indicate that the LMN is functioning properly.

The most common superficial reflex in the neurological exam is the **plantar reflex** that tests for the **Babinski sign** on the basis of the extension or flexion of the toes at the plantar surface of the foot. The plantar reflex is commonly tested in newborn infants to establish the presence of neuromuscular function. To elicit this reflex, an examiner brushes a stimulus, usually the examiner's fingertip, along the plantar surface of the infant's foot. An infant would present a positive Babinski sign, meaning the foot dorsiflexes and the toes extend and splay out. As a person learns to walk, the plantar reflex changes to cause curling of the toes and a moderate plantar flexion. If superficial stimulation of the sole of the foot caused extension of the foot, keeping one's balance would be harder. The descending input of the corticospinal tract modifies the response of the plantar reflex, meaning that a negative Babinski sign is the expected response in testing the reflex. Other superficial reflexes are not commonly tested, though a series of abdominal reflexes can target function in the lower thoracic spinal segments.

## INTERACTIVE LINK

Watch this [video](http://openstax.org/l/reflexttest) (<http://openstax.org/l/reflexttest>) to see how to test reflexes in the abdomen. Testing reflexes of the trunk is not commonly performed in the neurological exam, but if findings suggest a problem with the thoracic segments of the spinal cord, a series of superficial reflexes of the abdomen can localize function to those segments. If contraction is not observed when the skin lateral to the umbilicus (belly button) is stimulated, what level of the spinal cord may be damaged?

### Comparison of Upper and Lower Motor Neuron Damage

Many of the tests of motor function can indicate differences that will address whether damage to the motor system is in the upper or lower motor neurons. Signs that suggest a UMN lesion include muscle weakness, strong deep tendon reflexes, decreased control of movement or slowness, pronator drift, a positive Babinski sign, **spasticity**, and the **clasp-knife response**. Spasticity is an excess contraction in resistance to stretch. It can result in **hyperflexia**, which is when joints are overly flexed. The clasp-knife response occurs when the patient initially resists movement, but then releases, and the joint will quickly flex like a pocket knife closing.

A lesion on the LMN would result in paralysis, or at least partial loss of voluntary muscle control, which is known as **paresis**. The paralysis observed in LMN diseases is referred to as **flaccid paralysis**, referring to a complete or partial loss of muscle tone, in contrast to the loss of control in UMN lesions in which tone is retained and spasticity is exhibited. Other signs of an LMN lesion are **fibrillation**, **fasciculation**, and compromised or lost reflexes resulting from the denervation of the muscle fibers.

### Disorders of the...

#### Spinal Cord

In certain situations, such as a motorcycle accident, only half of the spinal cord may be damaged in what is known as a hemisection. Forceful trauma to the trunk may cause ribs or vertebrae to fracture, and debris can crush or section through part of the spinal cord. The full section of a spinal cord would result in paraplegia, or loss of voluntary motor control of the lower body, as well as loss of sensations from that point down. A hemisection, however, will leave spinal cord tracts intact on one side. The resulting condition would be hemiplegia on the side of the trauma—one leg would be paralyzed. The sensory results are more complicated.

The ascending tracts in the spinal cord are segregated between the dorsal column and spinothalamic pathways. This means that the sensory deficits will be based on the particular sensory information each pathway conveys. Sensory discrimination between touch and painful stimuli will illustrate the difference in how these pathways divide these functions.

On the paralyzed leg, a patient will acknowledge painful stimuli, but not fine touch or proprioceptive sensations. On the functional leg, the opposite is true. The reason for this is that the dorsal column pathway ascends ipsilateral to the sensation, so it would be damaged the same way as the lateral corticospinal tract. The spinothalamic pathway decussates immediately upon entering the spinal cord and ascends contralateral to the source; it would therefore bypass the hemisection.

The motor system can indicate the loss of input to the ventral horn in the lumbar enlargement where motor neurons to the leg are found, but motor function in the trunk is less clear. The left and right anterior corticospinal tracts are directly adjacent to each other. The likelihood of trauma to the spinal cord resulting in a hemisection that affects one anterior column, but not the other, is very unlikely. Either the axial musculature will not be affected at all, or there will be bilateral losses in the trunk.

Sensory discrimination can pinpoint the level of damage in the spinal cord. Below the hemisection, pain stimuli will be perceived in the damaged side, but not fine touch. The opposite is true on the other side. The pain fibers on the side with motor function cross the midline in the spinal cord and ascend in the contralateral lateral column as far as the hemisection. The dorsal column will be intact ipsilateral to the source on the intact side and reach the brain for conscious perception. The trauma would be at the level just before sensory discrimination returns to normal, helping to pinpoint the trauma. Whereas imaging technology, like magnetic resonance

imaging (MRI) or computed tomography (CT) scanning, could localize the injury as well, nothing more complicated than a cotton-tipped applicator can localize the damage. That may be all that is available on the scene when moving the victim requires crucial decisions be made.

## 16.5 The Coordination and Gait Exams

### LEARNING OBJECTIVES

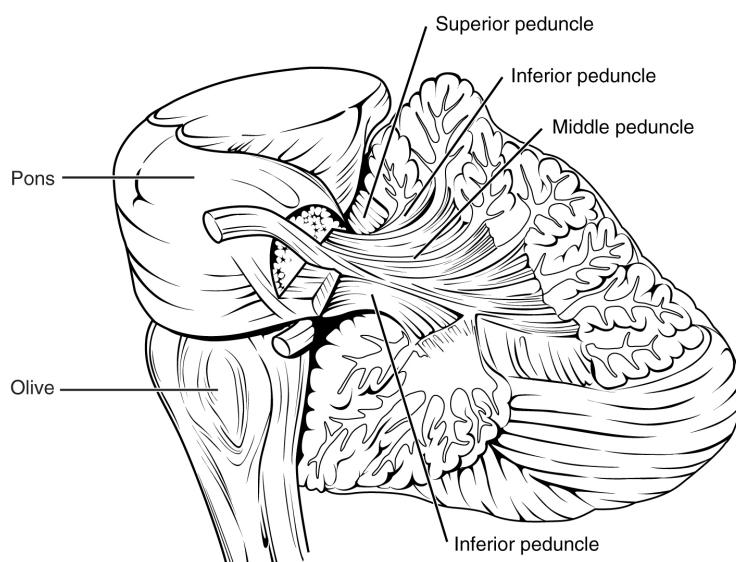
By the end of this section, you will be able to:

- Explain the relationship between the location of the cerebellum and its function in movement
- Chart the major divisions of the cerebellum
- List the major connections of the cerebellum
- Describe the relationship of the cerebellum to axial and appendicular musculature
- Explain the prevalent causes of cerebellar ataxia

The role of the cerebellum is a subject of debate. There is an obvious connection to motor function based on the clinical implications of cerebellar damage. There is also strong evidence of the cerebellar role in procedural memory. The two are not incompatible; in fact, procedural memory is motor memory, such as learning to ride a bicycle. Significant work has been performed to describe the connections within the cerebellum that result in learning. A model for this learning is classical conditioning, as shown by the famous dogs from the physiologist Ivan Pavlov's work. This classical conditioning, which can be related to motor learning, fits with the neural connections of the cerebellum. The cerebellum is 10 percent of the mass of the brain and has varied functions that all point to a role in the motor system.

### Location and Connections of the Cerebellum

The cerebellum is located in apposition to the dorsal surface of the brain stem, centered on the pons. The name of the pons is derived from its connection to the cerebellum. The word means "bridge" and refers to the thick bundle of myelinated axons that form a bulge on its ventral surface. Those fibers are axons that project from the gray matter of the pons into the contralateral cerebellar cortex. These fibers make up the **middle cerebellar peduncle (MCP)** and are the major physical connection of the cerebellum to the brain stem ([Figure 16.14](#)). Two other white matter bundles connect the cerebellum to the other regions of the brain stem. The **superior cerebellar peduncle (SCP)** is the connection of the cerebellum to the midbrain and forebrain. The **inferior cerebellar peduncle (ICP)** is the connection to the medulla.

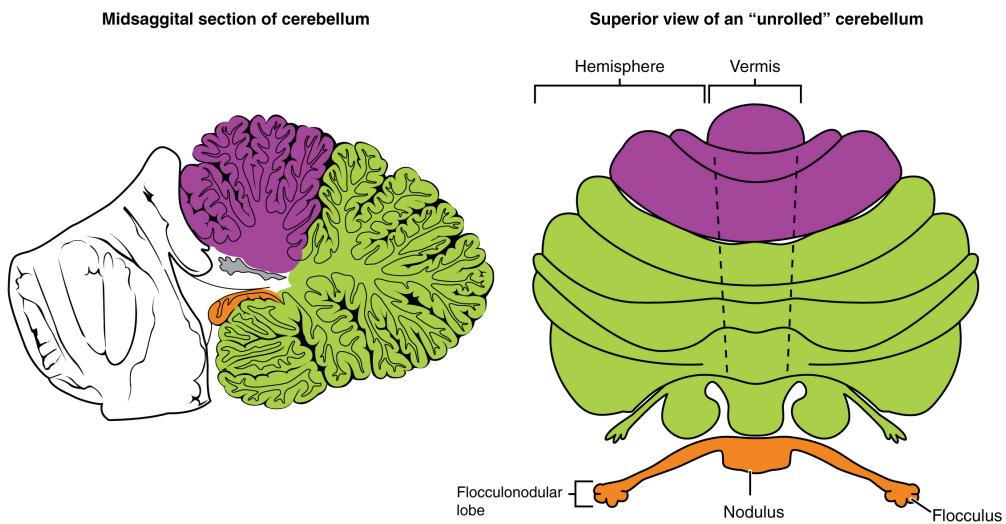


**FIGURE 16.14 Cerebellar Peduncles** The connections to the cerebellum are the three cerebellar peduncles, which are close to each other. The ICP arises from the medulla—specifically from the inferior olive, which is visible as a bulge on the ventral surface of the brain stem. The MCP is the ventral surface of the pons. The SCP projects into the midbrain.

These connections can also be broadly described by their functions. The ICP conveys sensory input to the

cerebellum, partially from the spinocerebellar tract, but also through fibers of the **inferior olive**. The MCP is part of the **cortico-ponto-cerebellar pathway** that connects the cerebral cortex with the cerebellum and preferentially targets the lateral regions of the cerebellum. It includes a copy of the motor commands sent from the precentral gyrus through the corticospinal tract, arising from collateral branches that synapse in the gray matter of the pons, along with input from other regions such as the visual cortex. The SCP is the major output of the cerebellum, divided between the **red nucleus** in the midbrain and the thalamus, which will return cerebellar processing to the motor cortex. These connections describe a circuit that compares motor commands and sensory feedback to generate a new output. These comparisons make it possible to coordinate movements. If the cerebral cortex sends a motor command to initiate walking, that command is copied by the pons and sent into the cerebellum through the MCP. Sensory feedback in the form of proprioception from the spinal cord, as well as vestibular sensations from the inner ear, enters through the ICP. If you take a step and begin to slip on the floor because it is wet, the output from the cerebellum—through the SCP—can correct for that and keep you balanced and moving. The red nucleus sends new motor commands to the spinal cord through the **rubrospinal tract**.

The cerebellum is divided into regions that are based on the particular functions and connections involved. The midline regions of the cerebellum, the **vermis** and **flocculonodular lobe**, are involved in comparing visual information, equilibrium, and proprioceptive feedback to maintain balance and coordinate movements such as walking, or **gait**, through the descending output of the red nucleus (Figure 16.15). The lateral hemispheres are primarily concerned with planning motor functions through frontal lobe inputs that are returned through the thalamic projections back to the premotor and motor cortices. Processing in the midline regions targets movements of the axial musculature, whereas the lateral regions target movements of the appendicular musculature. The vermis is referred to as the **spinocerebellum** because it primarily receives input from the dorsal columns and spinocerebellar pathways. The flocculonodular lobe is referred to as the **vestibulocerebellum** because of the vestibular projection into that region. Finally, the lateral cerebellum is referred to as the **cerebrocerebellum**, reflecting the significant input from the cerebral cortex through the cortico-ponto-cerebellar pathway.



**FIGURE 16.15 Major Regions of the Cerebellum** The cerebellum can be divided into two basic regions: the midline and the hemispheres. The midline is composed of the vermis and the flocculonodular lobe, and the hemispheres are the lateral regions.

### Coordination and Alternating Movement

Testing for cerebellar function is the basis of the coordination exam. The subtests target appendicular musculature, controlling the limbs, and axial musculature for posture and gait. The assessment of cerebellar function will depend on the normal functioning of other systems addressed in previous sections of the neurological exam. Motor control from the cerebrum, as well as sensory input from somatic, visual, and vestibular senses, are important to cerebellar function.

The subtests that address appendicular musculature, and therefore the lateral regions of the cerebellum, begin with a check for tremor. The patient extends their arms in front of them and holds the position. The examiner watches for the presence of tremors that would not be present if the muscles are relaxed. By pushing down on the arms in this position, the examiner can check for the rebound response, which is when the arms are automatically brought back

to the extended position. The extension of the arms is an ongoing motor process, and the tap or push on the arms presents a change in the proprioceptive feedback. The cerebellum compares the cerebral motor command with the proprioceptive feedback and adjusts the descending input to correct. The red nucleus would send an additional signal to the LMN for the arm to increase contraction momentarily to overcome the change and regain the original position.

The **check reflex** depends on cerebellar input to keep increased contraction from continuing after the removal of resistance. The patient flexes the elbow against resistance from the examiner to extend the elbow. When the examiner releases the arm, the patient should be able to stop the increased contraction and keep the arm from moving. A similar response would be seen if you try to pick up a coffee mug that you believe to be full but turns out to be empty. Without checking the contraction, the mug would be thrown from the overexertion of the muscles expecting to lift a heavier object.

Several subtests of the cerebellum assess the ability to alternate movements, or switch between muscle groups that may be antagonistic to each other. In the finger-to-nose test, the patient touches their finger to the examiner's finger and then to their nose, and then back to the examiner's finger, and back to the nose. The examiner moves the target finger to assess a range of movements. A similar test for the lower extremities has the patient touch their toe to a moving target, such as the examiner's finger. Both of these tests involve flexion and extension around a joint—the elbow or the knee and the shoulder or hip—as well as movements of the wrist and ankle. The patient must switch between the opposing muscles, like the biceps and triceps brachii, to move their finger from the target to their nose. Coordinating these movements involves the motor cortex communicating with the cerebellum through the pons and feedback through the thalamus to plan the movements. Visual cortex information is also part of the processing that occurs in the cerebrocerebellum while it is involved in guiding movements of the finger or toe.

Rapid, alternating movements are tested for the upper and lower extremities. The patient is asked to touch each finger to their thumb, or to pat the palm of one hand on the back of the other, and then flip that hand over and alternate back-and-forth. To test similar function in the lower extremities, the patient touches their heel to their shin near the knee and slides it down toward the ankle, and then back again, repetitively. Rapid, alternating movements are part of speech as well. A patient is asked to repeat the nonsense consonants “lah-kah-pah” to alternate movements of the tongue, lips, and palate. All of these rapid alternations require planning from the cerebrocerebellum to coordinate movement commands that control the coordination.

## Posture and Gait

Gait can either be considered a separate part of the neurological exam or a subtest of the coordination exam that addresses walking and balance. Testing posture and gait addresses functions of the spinocerebellum and the vestibulocerebellum because both are part of these activities. A subtest called station begins with the patient standing in a normal position to check for the placement of the feet and balance. The patient is asked to hop on one foot to assess the ability to maintain balance and posture during movement. Though the station subtest appears to be similar to the Romberg test, the difference is that the patient's eyes are open during station. The Romberg test has the patient stand still with the eyes closed. Any changes in posture would be the result of proprioceptive deficits, and the patient is able to recover when they open their eyes.

Subtests of walking begin with having the patient walk normally for a distance away from the examiner, and then turn and return to the starting position. The examiner watches for abnormal placement of the feet and the movement of the arms relative to the movement. The patient is then asked to walk with a few different variations. Tandem gait is when the patient places the heel of one foot against the toe of the other foot and walks in a straight line in that manner. Walking only on the heels or only on the toes will test additional aspects of balance.

## Ataxia

A movement disorder of the cerebellum is referred to as **ataxia**. It presents as a loss of coordination in voluntary movements. Ataxia can also refer to sensory deficits that cause balance problems, primarily in proprioception and equilibrium. When the problem is observed in movement, it is ascribed to cerebellar damage. Sensory and vestibular ataxia would likely also present with problems in gait and station.

Ataxia is often the result of exposure to exogenous substances, focal lesions, or a genetic disorder. Focal lesions include strokes affecting the cerebellar arteries, tumors that may impinge on the cerebellum, trauma to the back of

the head and neck, or MS. Alcohol intoxication or drugs such as ketamine cause ataxia, but it is often reversible. Mercury in fish can cause ataxia as well. Hereditary conditions can lead to degeneration of the cerebellum or spinal cord, as well as malformation of the brain, or the abnormal accumulation of copper seen in Wilson's disease.

## INTERACTIVE LINK

Watch this short [video](http://openstax.org/l/stationtest) (<http://openstax.org/l/stationtest>) to see a test for station. Station refers to the position a person adopts when they are standing still. The examiner would look for issues with balance, which coordinates proprioceptive, vestibular, and visual information in the cerebellum. To test the ability of a subject to maintain balance, asking them to stand or hop on one foot can be more demanding. The examiner may also push the subject to see if they can maintain balance. An abnormal finding in the test of station is if the feet are placed far apart. Why would a wide stance suggest problems with cerebellar function?

### Everyday Connection

#### The Field Sobriety Test

The neurological exam has been described as a clinical tool throughout this chapter. It is also useful in other ways. A variation of the coordination exam is the Field Sobriety Test (FST) used to assess whether drivers are under the influence of alcohol. The cerebellum is crucial for coordinated movements such as keeping balance while walking, or moving appendicular musculature on the basis of proprioceptive feedback. The cerebellum is also very sensitive to ethanol, the particular type of alcohol found in beer, wine, and liquor.

Walking in a straight line involves comparing the motor command from the primary motor cortex to the proprioceptive and vestibular sensory feedback, as well as following the visual guide of the white line on the side of the road. When the cerebellum is compromised by alcohol, the cerebellum cannot coordinate these movements effectively, and maintaining balance becomes difficult.

Another common aspect of the FST is to have the driver extend their arms out wide and touch their fingertip to their nose, usually with their eyes closed. The point of this is to remove the visual feedback for the movement and force the driver to rely just on proprioceptive information about the movement and position of their fingertip relative to their nose. With eyes open, the corrections to the movement of the arm might be so small as to be hard to see, but proprioceptive feedback is not as immediate and broader movements of the arm will probably be needed, particularly if the cerebellum is affected by alcohol.

Reciting the alphabet backwards is not always a component of the FST, but its relationship to neurological function is interesting. There is a cognitive aspect to remembering how the alphabet goes and how to recite it backwards. That is actually a variation of the mental status subtest of repeating the months backwards. However, the cerebellum is important because speech production is a coordinated activity. The speech rapid alternating movement subtest is specifically using the consonant changes of "lah-kah-pah" to assess coordinated movements of the lips, tongue, pharynx, and palate. But the entire alphabet, especially in the nonrehearsed backwards order, pushes this type of coordinated movement quite far. It is related to the reason that speech becomes slurred when a person is intoxicated.

## Key Terms

**accommodation** in vision, a change in the ability of the eye to focus on objects at different distances

**accommodation-convergence reflex** coordination of somatic control of the medial rectus muscles of either eye with the parasympathetic control of the ciliary bodies to maintain focus while the eyes converge on visual stimuli near to the face

**anterograde amnesia** inability to form new memories from a particular time forward

**aphasia** loss of language function

**ataxia** movement disorder related to damage of the cerebellum characterized by loss of coordination in voluntary movements

**Babinski sign** dorsiflexion of the foot with extension and splaying of the toes in response to the plantar reflex, normally suppressed by corticospinal input

**cerebrocerebellum** lateral regions of the cerebellum; named for the significant input from the cerebral cortex

**check reflex** response to a release in resistance so that the contractions stop, or check, movement

**clasp-knife response** sign of UMN disease when a patient initially resists passive movement of a muscle but will quickly release to a lower state of resistance

**conduction aphasia** loss of language function related to connecting the understanding of speech with the production of speech, without either specific function being lost

**conductive hearing** hearing dependent on the conduction of vibrations of the tympanic membrane through the ossicles of the middle ear

**conjugate gaze** coordinated movement of the two eyes simultaneously in the same direction

**convergence** in vision, the movement of the eyes so that they are both pointed at the same point in space, which increases for stimuli that are closer to the subject

**coordination exam** major section of the neurological exam that assesses complex, coordinated motor functions of the cerebellum and associated motor pathways

**cortico-ponto-cerebellar pathway** projection from the cerebral cortex to the cerebellum by way of the gray matter of the pons

**cranial nerve exam** major section of the neurological exam that assesses sensory and motor functions of the cranial nerves and their associated central and peripheral structures

**cytoarchitecture** study of a tissue based on the structure and organization of its cellular components; related to the broader term, histology

**deep tendon reflex** another term for stretch reflex, based on the elicitation through deep stimulation of the tendon at the insertion

**diplopia** double vision resulting from a failure in conjugate gaze

**edema** fluid accumulation in tissue; often associated with circulatory deficits

**embolus** obstruction in a blood vessel such as a blood clot, fatty mass, air bubble, or other foreign matter that interrupts the flow of blood to an organ or some part of the body

**episodic memory** memory of specific events in an autobiographical sense

**expressive aphasia** loss of the ability to produce language; usually associated with damage to Broca's area in the frontal lobe

**extrinsic muscles of the tongue** muscles that are connected to other structures, such as the hyoid bone or the mandible, and control the position of the tongue

**fasciculation** small muscle twitch as a result of spontaneous activity from an LMN

**fauces** opening from the oral cavity into the pharynx

**fibrillation** in motor responses, a spontaneous muscle action potential that occurs in the absence of neuromuscular input, resulting from LMN lesions

**flaccid paralysis** loss of voluntary muscle control and muscle tone, as the result of LMN disease

**flaccidity** presentation of a loss of muscle tone, observed as floppy limbs or a lack of resistance to passive movement

**flocculonodular lobe** lobe of the cerebellum that receives input from the vestibular system to help with balance and posture

**gait** rhythmic pattern of alternating movements of the lower limbs during locomotion

**gait exam** major section of the neurological exam that assesses the cerebellum and descending pathways in the spinal cord through the coordinated motor functions of walking; a portion of the coordination exam

**gnosis** in a neurological exam, intuitive experiential knowledge tested by interacting with common objects or symbols

**graphesthesia** perception of symbols, such as letters or numbers, traced in the palm of the hand

**hemisection** cut through half of a structure, such as the spinal cord

**hemorrhagic stroke** disruption of blood flow to the brain caused by bleeding within the cranial vault

**hyperflexia** overly flexed joints

**hypotonicity** low muscle tone, a sign of LMN disease

- hypovolemia** decrease in blood volume
- inferior cerebellar peduncle (ICP)** input to the cerebellum, largely from the inferior olive, that represents sensory feedback from the periphery
- inferior olive** large nucleus in the medulla that receives input from sensory systems and projects into the cerebellar cortex
- internuclear ophthalmoplegia** deficit of conjugate lateral gaze because the lateral rectus muscle of one eye does not contract resulting from damage to the abducens nerve or the MLF
- intorsion** medial rotation of the eye around its axis
- intrinsic muscles of the tongue** muscles that originate out of, and insert into, other tissues within the tongue and control the shape of the tongue
- ischemic stroke** disruption of blood flow to the brain because blood cannot flow through blood vessels as a result of a blockage or narrowing of the vessel
- jaw-jerk reflex** stretch reflex of the masseter muscle
- localization of function** principle that circumscribed anatomical locations are responsible for specific functions in an organ system
- medial longitudinal fasciculus (MLF)** fiber pathway that connects structures involved in the control of eye and head position, from the superior colliculus to the vestibular nuclei and cerebellum
- mental status exam** major section of the neurological exam that assesses cognitive functions of the cerebrum
- middle cerebellar peduncle (MCP)** large, white-matter bridge from the pons that constitutes the major input to the cerebellar cortex
- motor exam** major section of the neurological exam that assesses motor functions of the spinal cord and spinal nerves
- neurological exam** clinical assessment tool that can be used to quickly evaluate neurological function and determine if specific parts of the nervous system have been affected by damage or disease
- paramedian pontine reticular formation (PPRF)** region of the brain stem adjacent to the motor nuclei for gaze control that coordinates rapid, conjugate eye movements
- paresis** partial loss of, or impaired, voluntary muscle control
- plantar reflex** superficial reflex initiated by gentle stimulation of the sole of the foot
- praxis** in a neurological exam, the act of doing something using ready knowledge or skills in response to verbal instruction
- procedural memory** memory of how to perform a specific task
- pronator drift** sign of contralateral corticospinal lesion when the one arm will drift into a pronated position when held straight out with the palms facing upward
- receptive aphasia** loss of the ability to understand received language, such as what is spoken to the subject or given in written form
- red nucleus** nucleus in the midbrain that receives output from the cerebellum and projects onto the spinal cord in the rubrospinal tract
- retrograde amnesia** loss of memories before a particular event
- Rinne test** use of a tuning fork to test conductive hearing loss versus sensorineural hearing loss
- Romberg test** test of equilibrium that requires the patient to maintain a straight, upright posture without visual feedback of position
- rubrospinal tract** descending tract from the red nucleus of the midbrain that results in modification of ongoing motor programs
- saccade** small, rapid movement of the eyes used to locate and direct the fovea onto visual stimuli
- sensorineural hearing** hearing dependent on the transduction and propagation of auditory information through the neural components of the peripheral auditory structures
- sensory exam** major section of the neurological exam that assesses sensory functions of the spinal cord and spinal nerves
- short-term memory** capacity to retain information actively in the brain for a brief period of time
- Snellen chart** standardized arrangement of letters in decreasing size presented to a subject at a distance of 20 feet to test visual acuity
- spasticity** increased contraction of a muscle in response to resistance, often resulting in hyperflexia
- spinocerebellar tract** ascending fibers that carry proprioceptive input to the cerebellum used in maintaining balance and coordinated movement
- spinocerebellum** midline region of the cerebellum known as the vermis that receives proprioceptive input from the spinal cord
- stereognosis** perception of common objects placed in the hand solely on the basis of manipulation of that object in the hand
- stroke** (also, cerebrovascular accident (CVA)) loss of neurological function caused by an interruption of blood flow to a region of the central nervous system
- superficial reflex** reflexive contraction initiated by gentle stimulation of the skin
- superior cerebellar peduncle (SCP)** white-matter tract representing output of the cerebellum to the red nucleus of the midbrain
- transient ischemic attack (TIA)** temporary

disruption of blood flow to the brain in which symptoms occur rapidly but last only a short time

**vermis** prominent ridge along the midline of the cerebellum that is referred to as the spinocerebellum

**vestibulo-ocular reflex (VOR)** reflex based on connections between the vestibular system and the cranial nerves of eye movements that ensures that images are stabilized on the retina as the head and body move

## Chapter Review

### 16.1 Overview of the Neurological Exam

The neurological exam is a clinical assessment tool to determine the extent of function from the nervous system. It is divided into five major sections that each deal with a specific region of the CNS. The mental status exam is concerned with the cerebrum and assesses higher functions such as memory, language, and emotion. The cranial nerve exam tests the functions of all of the cranial nerves and, therefore, their connections to the CNS through the forebrain and brain stem. The sensory and motor exams assess those functions as they relate to the spinal cord, as well as the combination of the functions in spinal reflexes. The coordination exam targets cerebellar function in coordinated movements, including those functions associated with gait.

Damage to and disease of the nervous system lead to loss of function. The location of the injury will correspond to the functional loss, as suggested by the principle of localization of function. The neurological exam provides the opportunity for a clinician to determine where damage has occurred on the basis of the function that is lost. Damage from acute injuries such as strokes may result in specific functions being lost, whereas broader effects in infection or developmental disorders may result in general losses across an entire section of the neurological exam.

### 16.2 The Mental Status Exam

The cerebrum, particularly the cerebral cortex, is the location of important cognitive functions that are the focus of the mental status exam. The regionalization of the cortex, initially described on the basis of anatomical evidence of cytoarchitecture, reveals the distribution of functionally distinct areas. Cortical regions can be described as primary sensory or motor areas, association areas, or multimodal integration areas. The functions attributed to these regions include attention, memory, language, speech, sensation, judgment, and abstract reasoning.

**vestibulocerebellum** flocculonodular lobe of the cerebellum named for the vestibular input from the eighth cranial nerve

**Weber test** use of a tuning fork to test the laterality of hearing loss by placing it at several locations on the midline of the skull

**Wernicke's area** region at the posterior end of the lateral sulcus in which speech comprehension is localized

The mental status exam addresses these cognitive abilities through a series of subtests designed to elicit particular behaviors ascribed to these functions. The loss of neurological function can illustrate the location of damage to the cerebrum. Memory functions are attributed to the temporal lobe, particularly the medial temporal lobe structures known as the hippocampus and amygdala, along with the adjacent cortex. Evidence of the importance of these structures comes from the side effects of a bilateral temporal lobectomy that were studied in detail in patient HM.

Losses of language and speech functions, known as aphasias, are associated with damage to the important integration areas in the left hemisphere known as Broca's or Wernicke's areas, as well as the connections in the white matter between them. Different types of aphasia are named for the particular structures that are damaged. Assessment of the functions of the sensorium includes praxis and gnosis. The subtests related to these functions depend on multimodal integration, as well as language-dependent processing.

The prefrontal cortex contains structures important for planning, judgment, reasoning, and working memory. Damage to these areas can result in changes to personality, mood, and behavior. The famous case of Phineas Gage suggests a role for this cortex in personality, as does the outdated practice of prefrontal lobectomy.

### 16.3 The Cranial Nerve Exam

The cranial nerves can be separated into four major groups associated with the subtests of the cranial nerve exam. First are the sensory nerves, then the nerves that control eye movement, the nerves of the oral cavity and superior pharynx, and the nerve that controls movements of the neck.

The olfactory, optic, and vestibulocochlear nerves are strictly sensory nerves for smell, sight, and balance and hearing, whereas the trigeminal, facial, and glossopharyngeal nerves carry somatosensation of the

face, and taste—separated between the anterior two-thirds of the tongue and the posterior one-third. Special senses are tested by presenting the particular stimuli to each receptive organ. General senses can be tested through sensory discrimination of touch versus painful stimuli.

The oculomotor, trochlear, and abducens nerves control the extraocular muscles and are connected by the medial longitudinal fasciculus to coordinate gaze. Testing conjugate gaze is as simple as having the patient follow a visual target, like a pen tip, through the visual field ending with an approach toward the face to test convergence and accommodation. Along with the vestibular functions of the eighth nerve, the vestibulo-ocular reflex stabilizes gaze during head movements by coordinating equilibrium sensations with the eye movement systems.

The trigeminal nerve controls the muscles of chewing, which are tested for stretch reflexes. Motor functions of the facial nerve are usually obvious if facial expressions are compromised, but can be tested by having the patient raise their eyebrows, smile, and frown. Movements of the tongue, soft palate, or superior pharynx can be observed directly while the patient swallows, while the gag reflex is elicited, or while the patient says repetitive consonant sounds. The motor control of the gag reflex is largely controlled by fibers in the vagus nerve and constitutes a test of that nerve because the parasympathetic functions of that nerve are involved in visceral regulation, such as regulating the heartbeat and digestion.

Movement of the head and neck using the sternocleidomastoid and trapezius muscles is controlled by the accessory nerve. Flexing of the neck and strength testing of those muscles reviews the function of that nerve.

#### 16.4 The Sensory and Motor Exams

The sensory and motor exams assess function related to the spinal cord and the nerves connected to it. Sensory functions are associated with the dorsal regions of the spinal cord, whereas motor function is associated with the ventral side. Localizing damage to the spinal cord is related to assessments of the peripheral projections mapped to dermatomes.

Sensory tests address the various submodalities of the somatic senses: touch, temperature, vibration, pain, and proprioception. Results of the subtests can point to trauma in the spinal cord gray matter, white matter, or

even in connections to the cerebral cortex.

Motor tests focus on the function of the muscles and the connections of the descending motor pathway. Muscle tone and strength are tested for upper and lower extremities. Input to the muscles comes from the descending cortical input of upper motor neurons and the direct innervation of lower motor neurons.

Reflexes can either be based on deep stimulation of tendons or superficial stimulation of the skin. The presence of reflexive contractions helps to differentiate motor disorders between the upper and lower motor neurons. The specific signs associated with motor disorders can establish the difference further, based on the type of paralysis, the state of muscle tone, and specific indicators such as pronator drift or the Babinski sign.

#### 16.5 The Coordination and Gait Exams

The cerebellum is an important part of motor function in the nervous system. It apparently plays a role in procedural learning, which would include motor skills such as riding a bike or throwing a football. The basis for these roles is likely to be tied into the role the cerebellum plays as a comparator for voluntary movement.

The motor commands from the cerebral hemispheres travel along the corticospinal pathway, which passes through the pons. Collateral branches of these fibers synapse on neurons in the pons, which then project into the cerebellar cortex through the middle cerebellar peduncles. Ascending sensory feedback, entering through the inferior cerebellar peduncles, provides information about motor performance. The cerebellar cortex compares the command to the actual performance and can adjust the descending input to compensate for any mismatch. The output from deep cerebellar nuclei projects through the superior cerebellar peduncles to initiate descending signals from the red nucleus to the spinal cord.

The primary role of the cerebellum in relation to the spinal cord is through the spinocerebellum; it controls posture and gait with significant input from the vestibular system. Deficits in cerebellar function result in ataxias, or a specific kind of movement disorder. The root cause of the ataxia may be the sensory input—either the proprioceptive input from the spinal cord or the equilibrium input from the vestibular system, or direct damage to the cerebellum by stroke, trauma, hereditary factors, or toxins.

## Interactive Link Questions

1. Watch this [video](http://openstax.org/l/neuroexam) (<http://openstax.org/l/neuroexam>) that provides a demonstration of the neurological exam—a series of tests that can be performed rapidly when a patient is initially brought into an emergency department. The exam can be repeated on a regular basis to keep a record of how and if neurological function changes over time. In what order were the sections of the neurological exam tested in this video, and which section seemed to be left out?
2. Watch this [video](http://openstax.org/l/neuroexam2) (<http://openstax.org/l/neuroexam2>) for an introduction to the neurological exam. Studying the neurological exam can give insight into how structure and function in the nervous system are interdependent. This is a tool both in the clinic and in the classroom, but for different reasons. In the clinic, this is a powerful but simple tool to assess a patient's neurological function. In the classroom, it is a different way to think about the nervous system. Though medical technology provides noninvasive imaging and real-time functional data, the presenter says these cannot replace the history at the core of the medical examination. What does history mean in the context of medical practice?
3. Read this [article](http://openstax.org/l/3word) (<http://openstax.org/l/3word>) to learn about a young man who texts his fiancée in a panic as he finds that he is having trouble remembering things. At the hospital, a neurologist administers the mental status exam, which is mostly normal except for the three-word recall test. The young man could not recall them even 30 seconds after hearing them and repeating them back to the doctor. An undiscovered mass in the mediastinum region was found to be Hodgkin's lymphoma, a type of cancer that affects the immune system and likely caused antibodies to attack the nervous system. The patient eventually regained his ability to remember, though the events in the hospital were always elusive. Considering that the effects on memory were temporary, but resulted in the loss of the specific events of the hospital stay, what regions of the brain were likely to have been affected by the antibodies and what type of memory does that represent?
4. Watch the [video](http://openstax.org/l/2brains) (<http://openstax.org/l/2brains>) titled "The Man With Two Brains" to see the neuroscientist Michael Gazzaniga introduce a patient he has worked with for years who has had his corpus callosum cut, separating his two cerebral hemispheres. A few tests are run to demonstrate how this manifests in tests of cerebral function. Unlike normal people, this patient can perform two independent tasks at the same time because the lines of communication between the right and left sides of his brain have been removed. Whereas a person with an intact corpus callosum cannot overcome the dominance of one hemisphere over the other, this patient can. If the left cerebral hemisphere is dominant in the majority of people, why would right-handedness be most common?
5. Watch this short [video](http://openstax.org/l/facialnerve) (<http://openstax.org/l/facialnerve>) to see an examination of the facial nerve using some simple tests. The facial nerve controls the muscles of facial expression. Severe deficits will be obvious in watching someone use those muscles for normal control. One side of the face might not move like the other side. But directed tests, especially for contraction against resistance, require a formal testing of the muscles. The muscles of the upper and lower face need to be tested. The strength test in this video involves the patient squeezing her eyes shut and the examiner trying to pry her eyes open. Why does the examiner ask her to try a second time?
6. Watch this [video](http://openstax.org/l/2point) (<http://openstax.org/l/2point>) to see a quick demonstration of two-point discrimination. Touching a specialized caliper to the surface of the skin will measure the distance between two points that are perceived as distinct stimuli versus a single stimulus. The patient keeps their eyes closed while the examiner switches between using both points of the caliper or just one. The patient then must indicate whether one or two stimuli are in contact with the skin. Why is the distance between the caliper points closer on the fingertips as opposed to the palm of the hand? And what do you think the distance would be on the arm, or the shoulder?

- 7.** Watch this [video](http://openstax.org/l/reflextest) (<http://openstax.org/l/reflextest>) to see how to test reflexes in the abdomen. Testing reflexes of the trunk is not commonly performed in the neurological exam, but if findings suggest a problem with the thoracic segments of the spinal cord, a series of superficial reflexes of the abdomen can localize function to those segments. If contraction is not observed when the skin lateral to the umbilicus (belly button) is stimulated, what level of the spinal cord may be damaged?
- 8.** Watch this short [video](http://openstax.org/l/stationtest) (<http://openstax.org/l/stationtest>) to see a test for station. Station refers to the position a person adopts when they are standing still. The examiner would look for issues with balance, which coordinates proprioceptive, vestibular, and visual information in the cerebellum. To test the ability of a subject to maintain balance, asking them to stand or hop on one foot can be more demanding. The examiner may also push the subject to see if they can maintain balance. An abnormal finding in the test of station is if the feet are placed far apart. Why would a wide stance suggest problems with cerebellar function?

## Review Questions

- 9.** Which major section of the neurological exam is *most likely* to reveal damage to the cerebellum?
- cranial nerve exam
  - mental status exam
  - sensory exam
  - coordination exam
- 10.** What function would *most likely* be affected by a restriction of a blood vessel in the cerebral cortex?
- language
  - gait
  - facial expressions
  - knee-jerk reflex
- 11.** Which major section of the neurological exam includes subtests that are sometimes considered a separate set of tests concerned with walking?
- mental status exam
  - cranial nerve exam
  - coordination exam
  - sensory exam
- 12.** Memory, emotional, language, and sensorimotor deficits together are *most likely* the result of what kind of damage?
- stroke
  - developmental disorder
  - whiplash
  - gunshot wound
- 13.** Where is language function localized in the majority of people?
- cerebellum
  - right cerebral hemisphere
  - hippocampus
  - left cerebral hemisphere
- 14.** Which of the following could be elements of cytoarchitecture, as related to Brodmann's microscopic studies of the cerebral cortex?
- connections to the cerebellum
  - activation by visual stimuli
  - number of neurons per square millimeter
  - number of gyri or sulci
- 15.** Which of the following could be a multimodal integrative area?
- primary visual cortex
  - premotor cortex
  - hippocampus
  - Wernicke's area
- 16.** Which is an example of episodic memory?
- how to bake a cake
  - your last birthday party
  - how old you are
  - needing to wear an oven mitt to take a cake out of the oven
- 17.** Which type of aphasia is more like hearing a foreign language spoken?
- receptive aphasia
  - expressive aphasia
  - conductive aphasia
  - Broca's aphasia
- 18.** What region of the cerebral cortex is associated with understanding language, both from another person and the language a person generates himself or herself?
- medial temporal lobe
  - ventromedial prefrontal cortex
  - superior temporal gyrus
  - postcentral gyrus

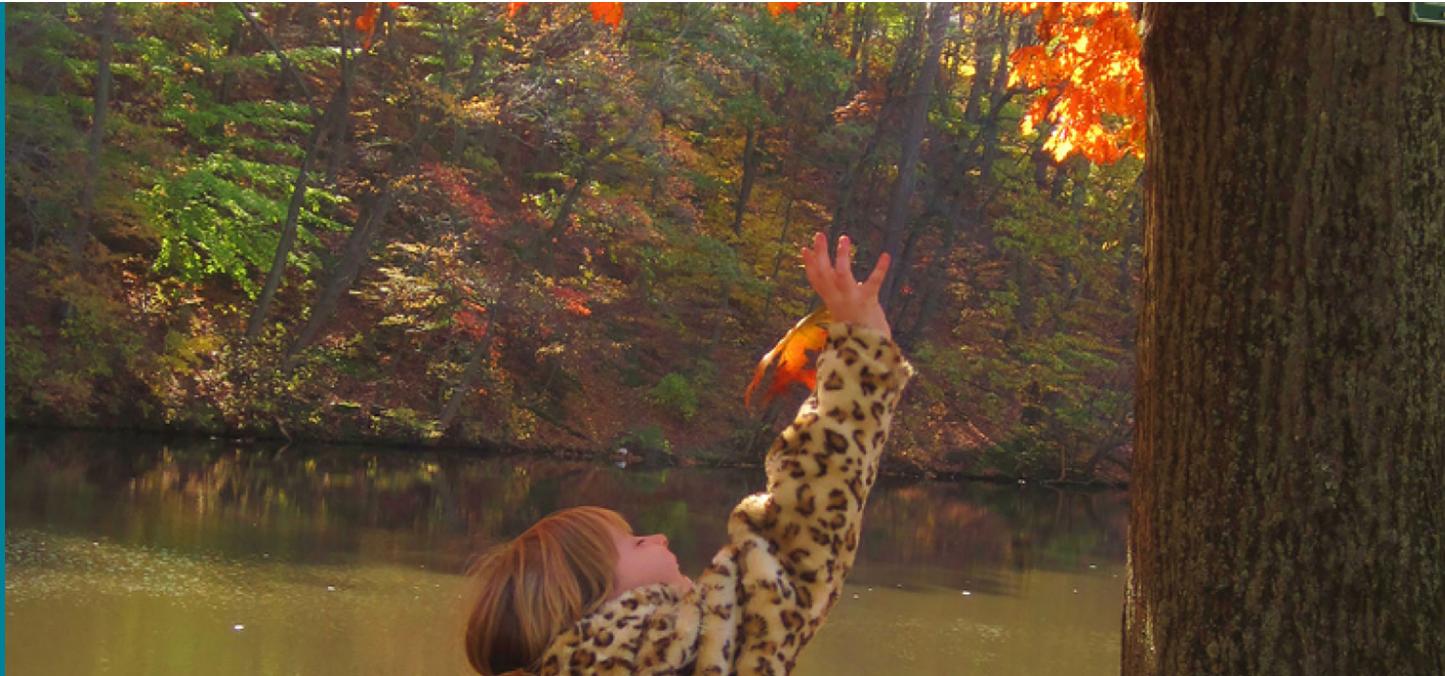
- 19.** Without olfactory sensation to complement gustatory stimuli, food will taste bland unless it is seasoned with which substance?
- salt
  - thyme
  - garlic
  - olive oil
- 20.** Which of the following cranial nerves is *not* part of the VOR?
- optic
  - oculomotor
  - abducens
  - vestibulocochlear
- 21.** Which nerve is responsible for controlling the muscles that result in the gag reflex?
- trigeminal
  - facial
  - glossopharyngeal
  - vagus
- 22.** Which nerve is responsible for taste, as well as salivation, in the anterior oral cavity?
- facial
  - glossopharyngeal
  - vagus
  - hypoglossal
- 23.** Which of the following nerves controls movements of the neck?
- oculomotor
  - vestibulocochlear
  - spinal accessory
  - hypoglossal
- 24.** Which of the following is *not* part of the corticospinal pathway?
- cerebellar deep white matter
  - midbrain
  - medulla
  - lateral column
- 25.** Which subtest is directed at proprioceptive sensation?
- two-point discrimination
  - tactile movement
  - vibration
  - Romberg test
- 26.** What term describes the inability to lift the arm above the level of the shoulder?
- paralysis
  - paresis
  - fasciculation
  - fibrillation
- 27.** Which type of reflex is the jaw-jerk reflex that is part of the cranial nerve exam for the vestibulocochlear nerve?
- visceral reflex
  - withdrawal reflex
  - stretch reflex
  - superficial reflex
- 28.** Which of the following is a feature of both somatic and visceral senses?
- requires cerebral input
  - causes skeletal muscle contraction
  - projects to a ganglion near the target effector
  - involves an axon in the ventral nerve root
- 29.** Which white matter structure carries information from the cerebral cortex to the cerebellum?
- cerebral peduncle
  - superior cerebellar peduncle
  - middle cerebellar peduncle
  - inferior cerebellar peduncle
- 30.** Which region of the cerebellum receives proprioceptive input from the spinal cord?
- vermis
  - left hemisphere
  - flocculonodular lobe
  - right hemisphere
- 31.** Which of the following tests cerebellar function related to gait?
- toe-to-finger
  - station
  - lah-kah-pah
  - finger-to-nose
- 32.** Which of the following is *not* a cause of cerebellar ataxia?
- mercury from fish
  - drinking alcohol
  - antibiotics
  - hereditary degeneration of the cerebellum
- 33.** Which of the following functions *cannot* be attributed to the cerebellum?
- comparing motor commands and sensory feedback
  - associating sensory stimuli with learned behavior
  - coordinating complex movements
  - processing visual information

## Critical Thinking Questions

34. Why is a rapid assessment of neurological function important in an emergency situation?
35. How is the diagnostic category of TIA different from a stroke?
36. A patient's performance of the majority of the mental status exam subtests is in line with the expected norms, but the patient cannot repeat a string of numbers given by the examiner. What is a likely explanation?
37. A patient responds to the question "What is your name?" with a look of incomprehension. Which of the two major language areas is most likely affected and what is the name for that type of aphasia?
38. As a person ages, their ability to focus on near objects (accommodation) changes. If a person is already myopic (near-sighted), why would corrective lenses not be necessary to read a book or computer screen?
39. When a patient flexes their neck, the head tips to the right side. Also, their tongue sticks out slightly to the left when they try to stick it straight out. Where is the damage to the brain stem most likely located?
40. The location of somatosensation is based on the topographical map of sensory innervation. What does this mean?
41. Why are upper motor neuron lesions characterized by "spastic paralysis"?
42. Learning to ride a bike is a motor function dependent on the cerebellum. Why are the different regions of the cerebellum involved in this complex motor learning?
43. Alcohol intoxication can produce slurred speech. How is this related to cerebellar function?

# CHAPTER 17

## The Endocrine System



**Figure 17.1 A Child Catches a Falling Leaf** Hormones of the endocrine system coordinate and control growth, metabolism, temperature regulation, the stress response, reproduction, and many other functions. (credit: "seenthroughmylense"/flickr.com)

### CHAPTER OBJECTIVES

After studying this chapter, you will be able to:

- Identify the contributions of the endocrine system to homeostasis
- Discuss the chemical composition of hormones and the mechanisms of hormone action
- Summarize the site of production, regulation, and effects of the hormones of the pituitary, thyroid, parathyroid, adrenal, and pineal glands
- Discuss the hormonal regulation of the reproductive system
- Explain the role of the pancreatic endocrine cells in the regulation of blood glucose
- Identify the hormones released by the heart, kidneys, and other organs with secondary endocrine functions
- Discuss several common diseases associated with endocrine system dysfunction
- Discuss the embryonic development of, and the effects of aging on, the endocrine system

**INTRODUCTION** You may never have thought of it this way, but when you send a text message to two friends to meet you at the dining hall at six, you’re sending digital signals that (you hope) will affect their behavior—even though they are some distance away. Similarly, certain cells send chemical signals to other cells in the body that influence their behavior. This long-distance intercellular communication, coordination, and control is critical for homeostasis, and it is the fundamental function of the endocrine system.

### 17.1 An Overview of the Endocrine System

#### LEARNING OBJECTIVES

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

- Distinguish the types of intercellular communication, their importance, mechanisms, and effects
- Identify the major organs and tissues of the endocrine system and their location in the body

Communication is a process in which a sender transmits signals to one or more receivers to control and coordinate actions. In the human body, two major organ systems participate in relatively “long distance” communication: the nervous system and the endocrine system. Together, these two systems are primarily responsible for maintaining

homeostasis in the body.

## Neural and Endocrine Signaling

The nervous system uses two types of intercellular communication—electrical and chemical signaling—either by the direct action of an electrical potential, or in the latter case, through the action of chemical neurotransmitters such as serotonin or norepinephrine. Neurotransmitters act locally and rapidly. When an electrical signal in the form of an action potential arrives at the synaptic terminal, they diffuse across the synaptic cleft (the gap between a sending neuron and a receiving neuron or muscle cell). Once the neurotransmitters interact (bind) with receptors on the receiving (post-synaptic) cell, the receptor stimulation is transduced into a response such as continued electrical signaling or modification of cellular response. The target cell responds within milliseconds of receiving the chemical “message”; this response then ceases very quickly once the neural signaling ends. In this way, neural communication enables body functions that involve quick, brief actions, such as movement, sensation, and cognition. In contrast, the **endocrine system** uses just one method of communication: chemical signaling. These signals are sent by the endocrine organs, which secrete chemicals—the **hormone**—into the extracellular fluid. Hormones are transported primarily via the bloodstream throughout the body, where they bind to receptors on target cells, inducing a characteristic response. As a result, endocrine signaling requires more time than neural signaling to prompt a response in target cells, though the precise amount of time varies with different hormones. For example, the hormones released when you are confronted with a dangerous or frightening situation, called the fight-or-flight response, occur by the release of adrenal hormones—epinephrine and norepinephrine—within seconds. In contrast, it may take up to 48 hours for target cells to respond to certain reproductive hormones.

### INTERACTIVE LINK

Visit this [link](http://openstax.org/l/hormonebind) (<http://openstax.org/l/hormonebind>) to watch an animation of the events that occur when a hormone binds to a cell membrane receptor. What is the secondary messenger made by adenylyl cyclase during the activation of liver cells by epinephrine?

In addition, endocrine signaling is typically less specific than neural signaling. The same hormone may play a role in a variety of different physiological processes depending on the target cells involved. For example, the hormone oxytocin promotes uterine contractions in people in labor. It is also important in breastfeeding, and may be involved in the sexual response and in feelings of emotional attachment in humans.

In general, the nervous system involves quick responses to rapid changes in the external environment, and the endocrine system is usually slower acting—taking care of the internal environment of the body, maintaining homeostasis, and controlling reproduction (Table 17.1). So how does the fight-or-flight response that was mentioned earlier happen so quickly if hormones are usually slower acting? It is because the two systems are connected. It is the fast action of the nervous system in response to the danger in the environment that stimulates the adrenal glands to secrete their hormones. As a result, the nervous system can cause rapid endocrine responses to keep up with sudden changes in both the external and internal environments when necessary.

### Endocrine and Nervous Systems

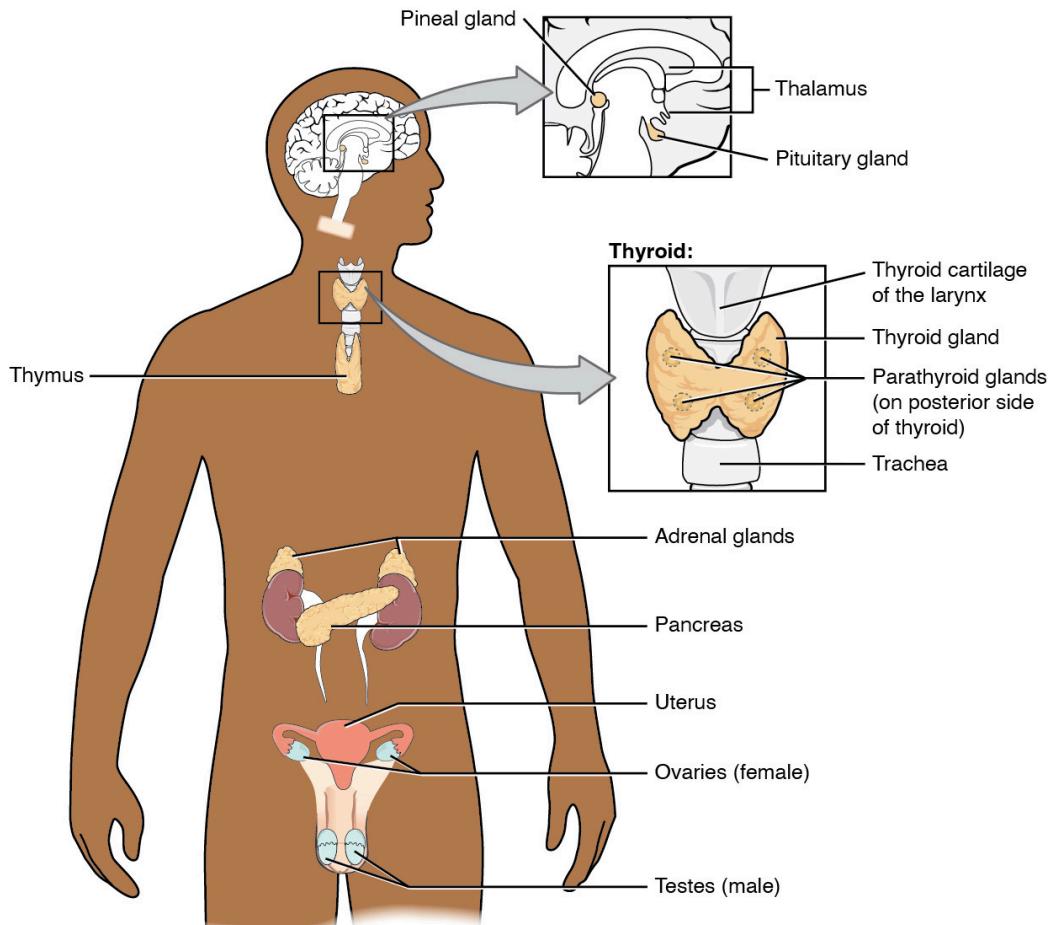
	Endocrine system	Nervous system
Signaling mechanism(s)	Chemical	Chemical/electrical
Primary chemical signal	Hormones	Neurotransmitters
Distance traveled	Long or short	Always short

TABLE 17.1

	Endocrine system	Nervous system
Response time	Fast or slow	Always fast
Environment targeted	Internal	Internal and external

**TABLE 17.1****Structures of the Endocrine System**

The endocrine system consists of cells, tissues, and organs that secrete hormones as a primary or secondary function. The **endocrine gland** is the major player in this system. The primary function of these ductless glands is to secrete their hormones directly into the surrounding fluid. The interstitial fluid and the blood vessels then transport the hormones throughout the body. The endocrine system includes the pituitary, thyroid, parathyroid, adrenal, and pineal glands (Figure 17.2). Some of these glands have both endocrine and non-endocrine functions. For example, the pancreas contains cells that function in digestion as well as cells that secrete the hormones insulin and glucagon, which regulate blood glucose levels. The hypothalamus, thymus, heart, kidneys, stomach, small intestine, liver, skin, ovaries, and testes are other organs that contain cells with endocrine function. Moreover, adipose tissue has long been known to produce hormones, and recent research has revealed that even bone tissue has endocrine functions.



**FIGURE 17.2 Endocrine System** Endocrine glands and cells are located throughout the body and play an important role in homeostasis.

The ductless endocrine glands are not to be confused with the body's **exocrine system**, whose glands release their secretions through ducts. Examples of exocrine glands include the sebaceous and sweat glands of the skin. As just noted, the pancreas also has an exocrine function: most of its cells secrete pancreatic juice through the pancreatic

and accessory ducts to the lumen of the small intestine.

### Other Types of Chemical Signaling

In endocrine signaling, hormones secreted into the extracellular fluid diffuse into the blood or lymph, and can then travel great distances throughout the body. In contrast, autocrine signaling takes place within the same cell. An **autocrine** (auto- = “self”) is a chemical that elicits a response in the same cell that secreted it. Interleukin-1, or IL-1, is a signaling molecule that plays an important role in inflammatory response. The cells that secrete IL-1 have receptors on their cell surface that bind these molecules, resulting in autocrine signaling.

Local intercellular communication is the province of the **paracrine**, also called a paracrine factor, which is a chemical that induces a response in neighboring cells. Although paracrines may enter the bloodstream, their concentration is generally too low to elicit a response from distant tissues. A familiar example to those with asthma is histamine, a paracrine that is released by immune cells in the bronchial tree. Histamine causes the smooth muscle cells of the bronchi to constrict, narrowing the airways. Another example is the neurotransmitters of the nervous system, which act only locally within the synaptic cleft.



### CAREER CONNECTION

#### Endocrinologist

Endocrinology is a specialty in the field of medicine that focuses on the treatment of endocrine system disorders. Endocrinologists—medical doctors who specialize in this field—are experts in treating diseases associated with hormonal systems, ranging from thyroid disease to diabetes mellitus. Endocrine surgeons treat endocrine disease through the removal, or resection, of the affected endocrine gland.

Patients who are referred to endocrinologists may have signs and symptoms or blood test results that suggest excessive or impaired functioning of an endocrine gland or endocrine cells. The endocrinologist may order additional blood tests to determine whether the patient’s hormonal levels are abnormal, or they may stimulate or suppress the function of the suspect endocrine gland and then have blood taken for analysis. Treatment varies according to the diagnosis. Some endocrine disorders, such as type 2 diabetes, may respond to lifestyle changes such as modest weight loss, adoption of a healthy diet, and regular physical activity. Other disorders may require medication, such as hormone replacement, and routine monitoring by the endocrinologist. These include disorders of the pituitary gland that can affect growth and disorders of the thyroid gland that can result in a variety of metabolic problems.

Some patients experience health problems as a result of the normal decline in hormones that can accompany aging. These patients can consult with an endocrinologist to weigh the risks and benefits of hormone replacement therapy intended to boost their natural levels of reproductive hormones.

In addition to treating patients, endocrinologists may be involved in research to improve the understanding of endocrine system disorders and develop new treatments for these diseases.

## 17.2 Hormones

### LEARNING OBJECTIVES

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

- Identify the three major classes of hormones on the basis of chemical structure
- Compare and contrast intracellular and cell membrane hormone receptors
- Describe signaling pathways that involve cAMP and IP<sub>3</sub>
- Identify several factors that influence a target cell’s response
- Discuss the role of feedback loops and humoral, hormonal, and neural stimuli in hormone control

Although a given hormone may travel throughout the body in the bloodstream, it will affect the activity only of its target cells; that is, cells with receptors for that particular hormone. Once the hormone binds to the receptor, a chain of events is initiated that leads to the target cell’s response. Hormones play a critical role in the regulation of physiological processes because of the target cell responses they regulate. These responses contribute to human reproduction, growth and development of body tissues, metabolism, fluid, and electrolyte balance, sleep, and many

other body functions. The major hormones of the human body and their effects are identified in [Table 17.2](#).

#### Endocrine Glands and Their Major Hormones

Endocrine gland	Associated hormones	Chemical class	Effect
Pituitary (anterior)	Growth hormone (GH)	Protein	Promotes growth of body tissues
Pituitary (anterior)	Prolactin (PRL)	Peptide	Promotes milk production
Pituitary (anterior)	Thyroid-stimulating hormone (TSH)	Glycoprotein	Stimulates thyroid hormone release
Pituitary (anterior)	Adrenocorticotropic hormone (ACTH)	Peptide	Stimulates hormone release by adrenal cortex
Pituitary (anterior)	Follicle-stimulating hormone (FSH)	Glycoprotein	Stimulates gamete production
Pituitary (anterior)	Luteinizing hormone (LH)	Glycoprotein	Stimulates androgen production by gonads
Pituitary (posterior)	Antidiuretic hormone (ADH)	Peptide	Stimulates water reabsorption by kidneys
Pituitary (posterior)	Oxytocin	Peptide	Stimulates uterine contractions during childbirth
Thyroid	Thyroxine (T <sub>4</sub> ), triiodothyronine (T <sub>3</sub> )	Amine	Stimulate basal metabolic rate
Thyroid	Calcitonin	Peptide	Reduces blood Ca <sup>2+</sup> levels
Parathyroid	Parathyroid hormone (PTH)	Peptide	Increases blood Ca <sup>2+</sup> levels
Adrenal (cortex)	Aldosterone	Steroid	Increases blood Na <sup>+</sup> levels
Adrenal (cortex)	Cortisol, corticosterone, cortisone	Steroid	Increase blood glucose levels
Adrenal (medulla)	Epinephrine, norepinephrine	Amine	Stimulate fight-or-flight response
Pineal	Melatonin	Amine	Regulates sleep cycles

**TABLE 17.2**

Endocrine gland	Associated hormones	Chemical class	Effect
Pancreas	Insulin	Protein	Reduces blood glucose levels
Pancreas	Glucagon	Protein	Increases blood glucose levels
Testes	Testosterone	Steroid	Stimulates development of sex characteristics including a deeper voice, increased muscle mass, development of body hair, and sperm production
Ovaries	Estrogens and progesterone	Steroid	Stimulate development of sex characteristics including the development of adipose and breast tissue, and prepare the body for childbirth

**TABLE 17.2****Types of Hormones**

The hormones of the human body can be divided into two major groups on the basis of their chemical structure. Hormones derived from amino acids include amines, peptides, and proteins. Those derived from lipids include steroids ([Figure 17.3](#)). These chemical groups affect a hormone's distribution, the type of receptors it binds to, and other aspects of its function.

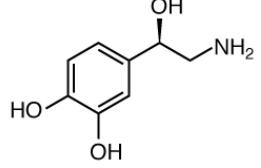
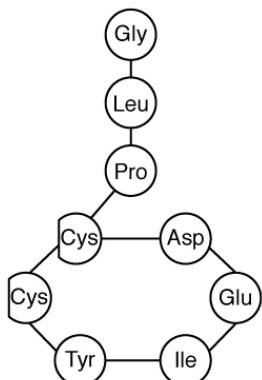
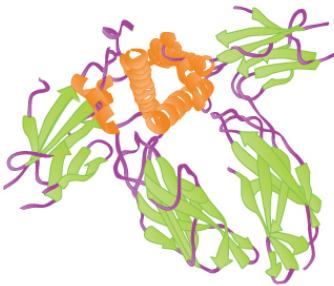
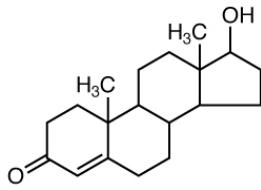
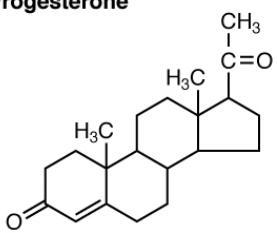
Hormone Class	Components	Example(s)
Amine Hormone	Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring)	<b>Norepinephrine</b> 
Peptide Hormone	Short chains of linked amino acids	<b>Oxytocin</b> 
Protein Hormone	Long chains of linked amino acids	<b>Human Growth Hormone</b> 
Steroid Hormones	Derived from the lipid cholesterol	<b>Testosterone</b>  <b>Progesterone</b> 

FIGURE 17.3 Amine, Peptide, Protein, and Steroid Hormone Structure

### Amine Hormones

Hormones derived from the modification of amino acids are referred to as amine hormones. Typically, the original structure of the amino acid is modified such that a  $-COOH$ , or carboxyl, group is removed, whereas the  $-NH_3^+$ , or amine, group remains.

Amine hormones are synthesized from the amino acids tryptophan or tyrosine. An example of a hormone derived from tryptophan is melatonin, which is secreted by the pineal gland and helps regulate circadian rhythm. Tyrosine derivatives include the metabolism-regulating thyroid hormones, as well as the catecholamines, such as epinephrine, norepinephrine, and dopamine. Epinephrine and norepinephrine are secreted by the adrenal medulla and play a role in the fight-or-flight response, whereas dopamine is secreted by the hypothalamus and inhibits the

release of certain anterior pituitary hormones.

### Peptide and Protein Hormones

Whereas the amine hormones are derived from a single amino acid, peptide and protein hormones consist of multiple amino acids that link to form an amino acid chain. Peptide hormones consist of short chains of amino acids, whereas protein hormones are longer polypeptides. Both types are synthesized like other body proteins: DNA is transcribed into mRNA, which is translated into an amino acid chain.

Examples of peptide hormones include antidiuretic hormone (ADH), a pituitary hormone important in fluid balance, and atrial-natriuretic peptide, which is produced by the heart and helps to decrease blood pressure. Some examples of protein hormones include growth hormone, which is produced by the pituitary gland, and follicle-stimulating hormone (FSH), which has an attached carbohydrate group and is thus classified as a glycoprotein. FSH helps stimulate the maturation of eggs in the ovaries and sperm in the testes.

### Steroid Hormones

The primary hormones derived from lipids are steroids. Steroid hormones are derived from the lipid cholesterol. For example, the reproductive hormones testosterone and the estrogens—which are produced by the gonads (testes and ovaries)—are steroid hormones. The adrenal glands produce the steroid hormone aldosterone, which is involved in osmoregulation, and cortisol, which plays a role in metabolism.

Like cholesterol, steroid hormones are not soluble in water (they are hydrophobic). Because blood is water-based, lipid-derived hormones must travel to their target cell bound to a transport protein. This more complex structure extends the half-life of steroid hormones much longer than that of hormones derived from amino acids. A hormone's half-life is the time required for half the concentration of the hormone to be degraded. For example, the lipid-derived hormone cortisol has a half-life of approximately 60 to 90 minutes. In contrast, the amino acid-derived hormone epinephrine has a half-life of approximately one minute.

### Pathways of Hormone Action

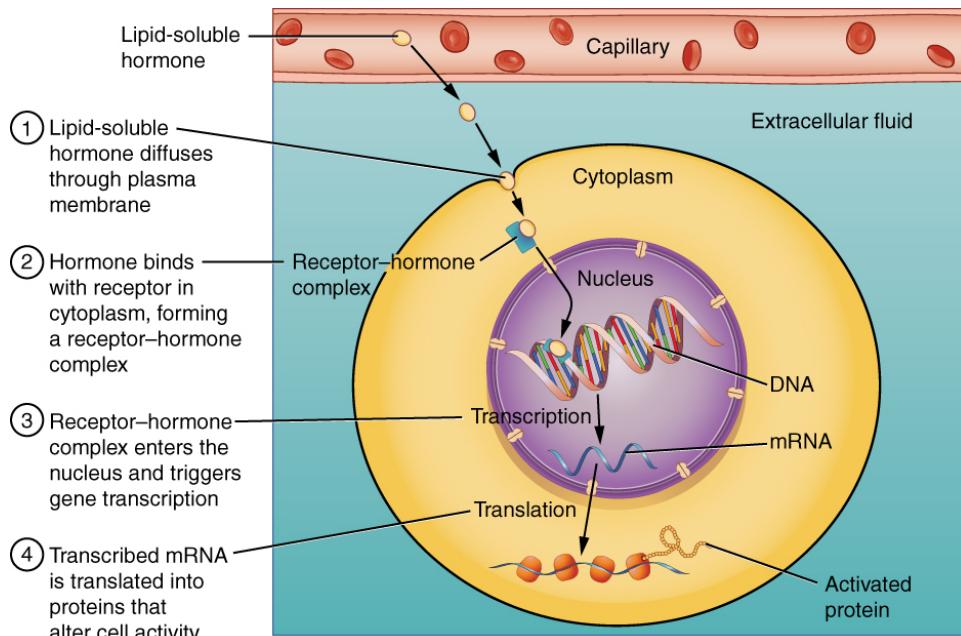
The message a hormone sends is received by a **hormone receptor**, a protein located either inside the cell or within the cell membrane. The receptor will process the message by initiating other signaling events or cellular mechanisms that result in the target cell's response. Hormone receptors recognize molecules with specific shapes and side groups, and respond only to those hormones that are recognized. The same type of receptor may be located on cells in different body tissues, and trigger somewhat different responses. Thus, the response triggered by a hormone depends not only on the hormone, but also on the target cell.

Once the target cell receives the hormone signal, it can respond in a variety of ways. The response may include the stimulation of protein synthesis, activation or deactivation of enzymes, alteration in the permeability of the cell membrane, altered rates of mitosis and cell growth, and stimulation of the secretion of products. Moreover, a single hormone may be capable of inducing different responses in a given cell.

### Pathways Involving Intracellular Hormone Receptors

Intracellular hormone receptors are located inside the cell. Hormones that bind to this type of receptor must be able to cross the cell membrane. Steroid hormones are derived from cholesterol and therefore can readily diffuse through the lipid bilayer of the cell membrane to reach the intracellular receptor ([Figure 17.4](#)). Thyroid hormones, cross the cell membrane by a specific carrier-mediated mechanism that is energy and  $\text{Na}^+$  dependent.

The location of steroid and thyroid hormone binding differs slightly: a steroid hormone may bind to its receptor within the cytosol or within the nucleus. In either case, this binding generates a hormone-receptor complex that moves toward the chromatin in the cell nucleus and binds to a particular segment of the cell's DNA. In contrast, thyroid hormones bind to receptors already bound to DNA. For both steroid and thyroid hormones, binding of the hormone-receptor complex with DNA triggers transcription of a target gene to mRNA, which moves to the cytosol and directs protein synthesis by ribosomes.

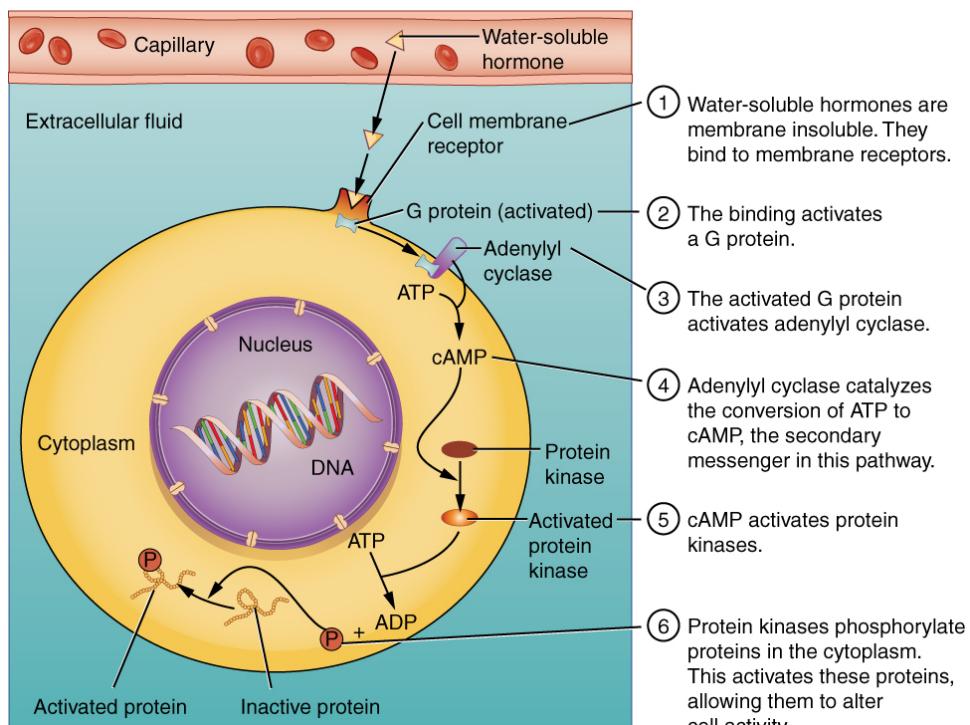


**FIGURE 17.4 Binding of Lipid-Soluble Hormones** A steroid hormone directly initiates the production of proteins within a target cell. Steroid hormones easily diffuse through the cell membrane. The hormone binds to its receptor in the cytosol, forming a receptor–hormone complex. The receptor–hormone complex then enters the nucleus and binds to the target gene on the DNA. Transcription of the gene creates a messenger RNA that is translated into the desired protein within the cytoplasm.

#### Pathways Involving Cell Membrane Hormone Receptors

Hydrophilic, or water-soluble, hormones are unable to diffuse through the lipid bilayer of the cell membrane and must therefore pass on their message to a receptor located at the surface of the cell. Except for thyroid hormones, which are lipid-soluble, all amino acid–derived hormones bind to cell membrane receptors that are located, at least in part, on the extracellular surface of the cell membrane. Therefore, they do not directly affect the transcription of target genes, but instead initiate a signaling cascade that is carried out by a molecule called a **second messenger**. In this case, the hormone is called a **first messenger**.

The second messenger used by most hormones is **cyclic adenosine monophosphate (cAMP)**. In the cAMP second messenger system, a water-soluble hormone binds to its receptor in the cell membrane (Step 1 in [Figure 17.5](#)). This receptor is associated with an intracellular component called a **G protein**, and binding of the hormone activates the G-protein component (Step 2). The activated G protein in turn activates an enzyme called **adenylyl cyclase**, also known as adenylate cyclase (Step 3), which converts adenosine triphosphate (ATP) to cAMP (Step 4). As the second messenger, cAMP activates a type of enzyme called a **protein kinase** that is present in the cytosol (Step 5). Activated protein kinases initiate a **phosphorylation cascade**, in which multiple protein kinases phosphorylate (add a phosphate group to) numerous and various cellular proteins, including other enzymes (Step 6).



**FIGURE 17.5 Binding of Water-Soluble Hormones** Water-soluble hormones cannot diffuse through the cell membrane. These hormones must bind to a surface cell-membrane receptor. The receptor then initiates a cell-signaling pathway within the cell involving G proteins, adenylyl cyclase, the secondary messenger cyclic AMP (cAMP), and protein kinases. In the final step, these protein kinases phosphorylate proteins in the cytoplasm. This activates proteins in the cell that carry out the changes specified by the hormone.

The phosphorylation of cellular proteins can trigger a wide variety of effects, from nutrient metabolism to the synthesis of different hormones and other products. The effects vary according to the type of target cell, the G proteins and kinases involved, and the phosphorylation of proteins. Examples of hormones that use cAMP as a second messenger include calcitonin, which is important for bone construction and regulating blood calcium levels; glucagon, which plays a role in blood glucose levels; and thyroid-stimulating hormone, which causes the release of  $T_3$  and  $T_4$  from the thyroid gland.

Overall, the phosphorylation cascade significantly increases the efficiency, speed, and specificity of the hormonal response, as thousands of signaling events can be initiated simultaneously in response to a very low concentration of hormone in the bloodstream. However, the duration of the hormone signal is short, as cAMP is quickly deactivated by the enzyme **phosphodiesterase (PDE)**, which is located in the cytosol. The action of PDE helps to ensure that a target cell's response ceases quickly unless new hormones arrive at the cell membrane.

Importantly, there are also G proteins that decrease the levels of cAMP in the cell in response to hormone binding. For example, when growth hormone-inhibiting hormone (GHIH), also known as somatostatin, binds to its receptors in the pituitary gland, the level of cAMP decreases, thereby inhibiting the secretion of human growth hormone.

Not all water-soluble hormones initiate the cAMP second messenger system. One common alternative system uses calcium ions as a second messenger. In this system, G proteins activate the enzyme phospholipase C (PLC), which functions similarly to adenylyl cyclase. Once activated, PLC cleaves a membrane-bound phospholipid into two molecules: **diacylglycerol (DAG)** and **inositol triphosphate ( $IP_3$ )**. Like cAMP, DAG activates protein kinases that initiate a phosphorylation cascade. At the same time,  $IP_3$  causes calcium ions to be released from storage sites within the cytosol, such as from within the smooth endoplasmic reticulum. The calcium ions then act as second messengers in two ways: they can influence enzymatic and other cellular activities directly, or they can bind to calcium-binding proteins, the most common of which is calmodulin. Upon binding calcium, calmodulin is able to modulate protein kinase within the cell. Examples of hormones that use calcium ions as a second messenger system include angiotensin II, which helps regulate blood pressure through vasoconstriction, and growth hormone-releasing hormone (GHRH), which causes the pituitary gland to release growth hormones.

## Factors Affecting Target Cell Response

You will recall that target cells must have receptors specific to a given hormone if that hormone is to trigger a response. But several other factors influence the target cell response. For example, the presence of a significant level of a hormone circulating in the bloodstream can cause its target cells to decrease their number of receptors for that hormone. This process is called **downregulation**, and it allows cells to become less reactive to the excessive hormone levels. When the level of a hormone is chronically reduced, target cells engage in **upregulation** to increase their number of receptors. This process allows cells to be more sensitive to the hormone that is present. Cells can also alter the sensitivity of the receptors themselves to various hormones.

Two or more hormones can interact to affect the response of cells in a variety of ways. The three most common types of interaction are as follows:

- The permissive effect, in which the presence of one hormone enables another hormone to act. For example, thyroid hormones have complex permissive relationships with certain reproductive hormones. A dietary deficiency of iodine, a component of thyroid hormones, can therefore affect reproductive system development and functioning.
- The synergistic effect, in which two hormones with similar effects produce an amplified response. In some cases, two hormones are required for an adequate response. For example, two different reproductive hormones—FSH from the pituitary gland and estrogens from the ovaries—are required for the maturation of female ova (egg cells).
- The antagonistic effect, in which two hormones have opposing effects. A familiar example is the effect of two pancreatic hormones, insulin and glucagon. Insulin increases the liver's storage of glucose as glycogen, decreasing blood glucose, whereas glucagon stimulates the breakdown of glycogen stores, increasing blood glucose.

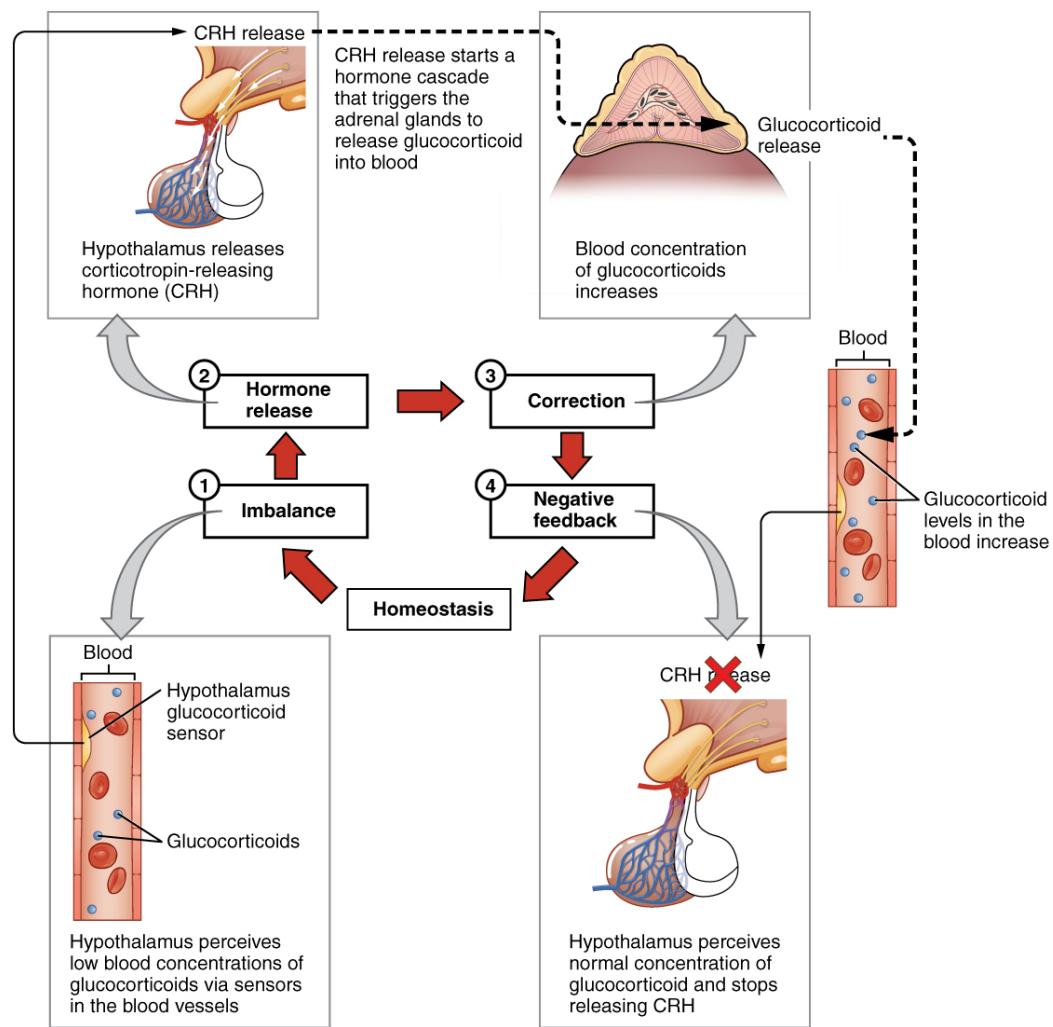
## Regulation of Hormone Secretion

To prevent abnormal hormone levels and a potential disease state, hormone levels must be tightly controlled. The body maintains this control by balancing hormone production and degradation. Feedback loops govern the initiation and maintenance of most hormone secretion in response to various stimuli.

### Role of Feedback Loops

The contribution of feedback loops to homeostasis will only be briefly reviewed here. Positive feedback loops are characterized by the release of additional hormone in response to an original hormone release. The release of oxytocin during childbirth is a positive feedback loop. The initial release of oxytocin begins to signal the uterine muscles to contract, which pushes the fetus toward the cervix, causing it to stretch. This, in turn, signals the pituitary gland to release more oxytocin, causing labor contractions to intensify. The release of oxytocin decreases after the birth of the child.

The more common method of hormone regulation is the negative feedback loop. Negative feedback is characterized by the inhibition of further secretion of a hormone in response to adequate levels of that hormone. This allows blood levels of the hormone to be regulated within a narrow range. An example of a negative feedback loop is the release of glucocorticoid hormones from the adrenal glands, as directed by the hypothalamus and pituitary gland. As glucocorticoid concentrations in the blood rise, the hypothalamus and pituitary gland reduce their signaling to the adrenal glands to prevent additional glucocorticoid secretion ([Figure 17.6](#)).



**FIGURE 17.6 Negative Feedback Loop** The release of adrenal glucocorticoids is stimulated by the release of hormones from the hypothalamus and pituitary gland. This signaling is inhibited when glucocorticoid levels become elevated by causing negative signals to the pituitary gland and hypothalamus.

### Role of Endocrine Gland Stimuli

Reflexes triggered by both chemical and neural stimuli control endocrine activity. These reflexes may be simple, involving only one hormone response, or they may be more complex and involve many hormones, as is the case with the hypothalamic control of various anterior pituitary-controlled hormones.

Humoral stimuli are changes in blood levels of non-hormone chemicals, such as nutrients or ions, which cause the release or inhibition of a hormone to, in turn, maintain homeostasis. For example, osmoreceptors in the hypothalamus detect changes in blood osmolarity (the concentration of solutes in the blood plasma). If blood osmolarity is too high, meaning that the blood is not dilute enough, osmoreceptors signal the hypothalamus to release ADH. The hormone causes the kidneys to reabsorb more water and reduce the volume of urine produced. This reabsorption causes a reduction of the osmolarity of the blood, diluting the blood to the appropriate level. The regulation of blood glucose is another example. High blood glucose levels cause the release of insulin from the pancreas, which increases glucose uptake by cells and liver storage of glucose as glycogen.

An endocrine gland may also secrete a hormone in response to the presence of another hormone produced by a different endocrine gland. Such hormonal stimuli often involve the hypothalamus, which produces releasing and inhibiting hormones that control the secretion of a variety of pituitary hormones.

In addition to these chemical signals, hormones can also be released in response to neural stimuli. A common example of neural stimuli is the activation of the fight-or-flight response by the sympathetic nervous system. When an individual perceives danger, sympathetic neurons signal the adrenal glands to secrete norepinephrine and

epinephrine. The two hormones dilate blood vessels, increase the heart and respiratory rate, and suppress the digestive and immune systems. These responses boost the body's transport of oxygen to the brain and muscles, thereby improving the body's ability to fight or flee.

### Everyday Connection

#### Bisphenol A and Endocrine Disruption

You may have heard news reports about the effects of a chemical called bisphenol A (BPA) in various types of food packaging. BPA is used in the manufacturing of hard plastics and epoxy resins. Common food-related items that may contain BPA include the lining of aluminum cans, plastic food-storage containers, drinking cups, as well as baby bottles and “sippy” cups. Other uses of BPA include medical equipment, dental fillings, and the lining of water pipes.

Research suggests that BPA is an endocrine disruptor, meaning that it negatively interferes with the endocrine system, particularly during the prenatal and postnatal development period. In particular, BPA mimics the hormonal effects of estrogens and has the opposite effect—that of androgens. The U.S. Food and Drug Administration (FDA) notes in their statement about BPA safety that although traditional toxicology studies have supported the safety of low levels of exposure to BPA, recent studies using novel approaches to test for subtle effects have led to some concern about the potential effects of BPA on the brain, behavior, and prostate gland in fetuses, infants, and young children. The FDA is currently facilitating decreased use of BPA in food-related materials. Many US companies have voluntarily removed BPA from baby bottles, “sippy” cups, and the linings of infant formula cans, and most plastic reusable water bottles sold today boast that they are “BPA free.” In contrast, both Canada and the European Union have completely banned the use of BPA in baby products.

The potential harmful effects of BPA have been studied in both animal models and humans and include a large variety of health effects, such as developmental delay and disease. For example, prenatal exposure to BPA during the first trimester of human pregnancy may be associated with wheezing and aggressive behavior during childhood. Adults exposed to high levels of BPA may experience altered thyroid signaling and male sexual dysfunction. BPA exposure during the prenatal or postnatal period of development in animal models has been observed to cause neurological delays, changes in brain structure and function, sexual dysfunction, asthma, and increased risk for multiple cancers. *In vitro* studies have also shown that BPA exposure causes molecular changes that initiate the development of cancers of the breast, prostate, and brain. Although these studies have implicated BPA in numerous ill health effects, some experts caution that some of these studies may be flawed and that more research needs to be done. In the meantime, the FDA recommends that consumers take precautions to limit their exposure to BPA. In addition to purchasing foods in packaging free of BPA, consumers should avoid carrying or storing foods or liquids in bottles with the recycling code 3 or 7. Foods and liquids should not be microwave-heated in any form of plastic: use paper, glass, or ceramics instead.

## 17.3 The Pituitary Gland and Hypothalamus

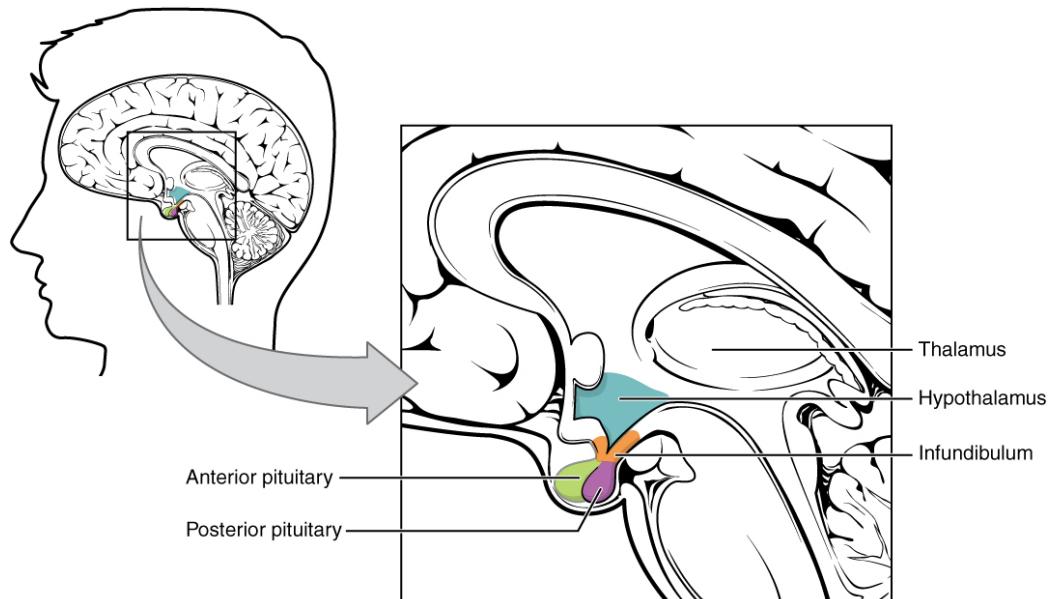
### LEARNING OBJECTIVES

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

- Explain the interrelationships of the anatomy and functions of the hypothalamus and the posterior and anterior lobes of the pituitary gland
- Identify the two hormones released from the posterior pituitary, their target cells, and their principal actions
- Identify the six hormones produced by the anterior lobe of the pituitary gland, their target cells, their principal actions, and their regulation by the hypothalamus

The hypothalamus–pituitary complex can be thought of as the “command center” of the endocrine system. This complex secretes several hormones that directly produce responses in target tissues, as well as hormones that regulate the synthesis and secretion of hormones of other glands. In addition, the hypothalamus–pituitary complex coordinates the messages of the endocrine and nervous systems. In many cases, a stimulus received by the nervous system must pass through the hypothalamus–pituitary complex to be translated into hormones that can initiate a response.

The **hypothalamus** is a structure of the diencephalon of the brain located anterior and inferior to the thalamus ([Figure 17.7](#)). It has both neural and endocrine functions, producing and secreting many hormones. In addition, the hypothalamus is anatomically and functionally related to the **pituitary gland** (or hypophysis), a bean-sized organ suspended from it by a stem called the **infundibulum** (or pituitary stalk). The pituitary gland is cradled within the sella turcica of the sphenoid bone of the skull. It consists of two lobes that arise from distinct parts of embryonic tissue: the posterior pituitary (neurohypophysis) is neural tissue, whereas the anterior pituitary (also known as the adenohypophysis) is glandular tissue that develops from the primitive digestive tract. The hormones secreted by the posterior and anterior pituitary, and the intermediate zone between the lobes are summarized in [Table 17.3](#).



**FIGURE 17.7 Hypothalamus–Pituitary Complex** The hypothalamus region lies inferior and anterior to the thalamus. It connects to the pituitary gland by the stalk-like infundibulum. The pituitary gland consists of an anterior and posterior lobe, with each lobe secreting different hormones in response to signals from the hypothalamus.

#### Pituitary Hormones

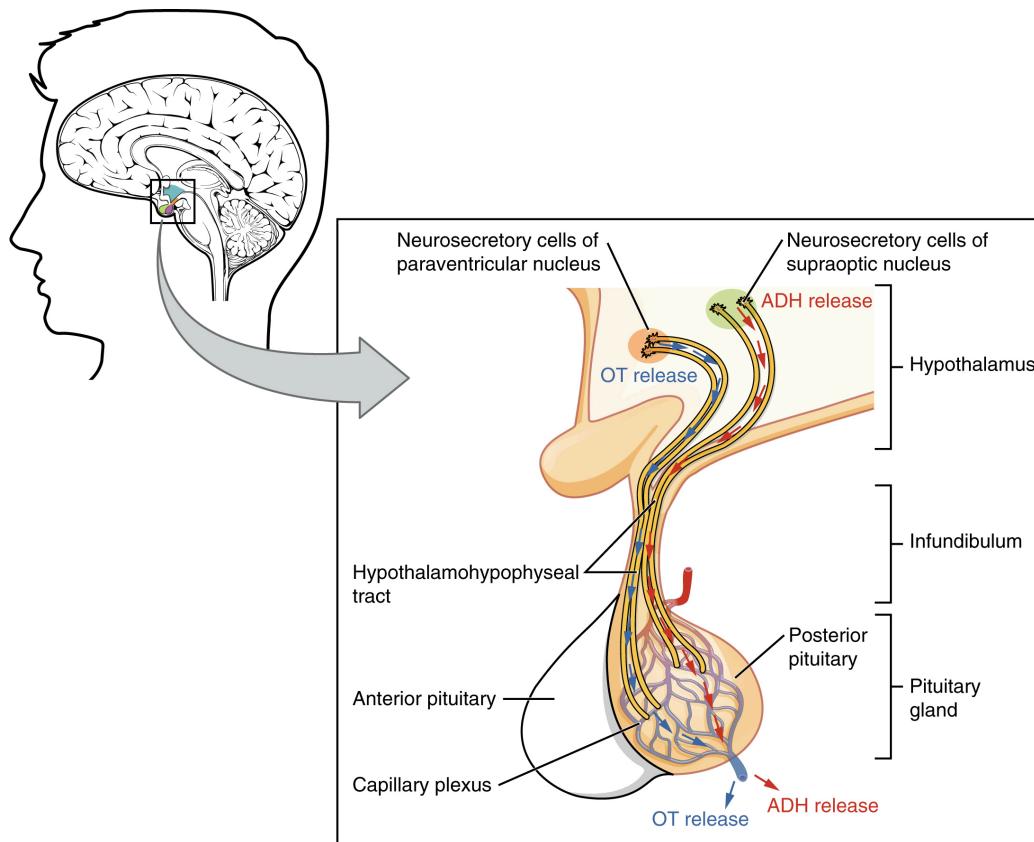
Pituitary lobe	Associated hormones	Chemical class	Effect
Anterior	Growth hormone (GH)	Protein	Promotes growth of body tissues
Anterior	Prolactin (PRL)	Peptide	Promotes milk production from mammary glands
Anterior	Thyroid-stimulating hormone (TSH)	Glycoprotein	Stimulates thyroid hormone release from thyroid
Anterior	Adrenocorticotropic hormone (ACTH)	Peptide	Stimulates hormone release by adrenal cortex
Anterior	Follicle-stimulating hormone (FSH)	Glycoprotein	Stimulates gamete production in gonads
Anterior	Luteinizing hormone (LH)	Glycoprotein	Stimulates androgen production by gonads

**TABLE 17.3**

Pituitary lobe	Associated hormones	Chemical class	Effect
Posterior	Antidiuretic hormone (ADH)	Peptide	Stimulates water reabsorption by kidneys
Posterior	Oxytocin	Peptide	Stimulates uterine contractions during childbirth
Intermediate zone	Melanocyte-stimulating hormone	Peptide	Stimulates melanin formation in melanocytes

**TABLE 17.3****Posterior Pituitary**

The posterior pituitary is actually an extension of the neurons of the paraventricular and supraoptic nuclei of the hypothalamus. The cell bodies of these regions rest in the hypothalamus, but their axons descend as the hypothalamic–hypophyseal tract within the infundibulum, and end in axon terminals that comprise the posterior pituitary ([Figure 17.8](#)).



**FIGURE 17.8 Posterior Pituitary** Neurosecretory cells in the hypothalamus release oxytocin (OT) or ADH into the posterior lobe of the pituitary gland. These hormones are stored or released into the blood via the capillary plexus.

The posterior pituitary gland does not produce hormones, but rather stores and secretes hormones produced by the hypothalamus. The paraventricular nuclei produce the hormone oxytocin, whereas the supraoptic nuclei produce ADH. These hormones travel along the axons into storage sites in the axon terminals of the posterior pituitary. In response to signals from the same hypothalamic neurons, the hormones are released from the axon terminals into the bloodstream.

### Oxytocin

When fetal development is complete, the peptide-derived hormone **oxytocin** (tocia- = “childbirth”) stimulates uterine contractions and dilation of the cervix. Throughout most of pregnancy, oxytocin hormone receptors are not expressed at high levels in the uterus. Toward the end of pregnancy, the synthesis of oxytocin receptors in the uterus increases, and the smooth muscle cells of the uterus become more sensitive to its effects. Oxytocin is continually released throughout childbirth through a positive feedback mechanism. As noted earlier, oxytocin prompts uterine contractions that push the fetal head toward the cervix. In response, cervical stretching stimulates additional oxytocin to be synthesized by the hypothalamus and released from the pituitary. This increases the intensity and effectiveness of uterine contractions and prompts additional dilation of the cervix. The feedback loop continues until birth.

Although the high blood levels of oxytocin begin to decrease immediately following birth, oxytocin continues to play a role in female and newborn health. First, oxytocin is necessary for the milk ejection reflex (commonly referred to as “let-down”) in breastfeeding people. As the newborn begins suckling, sensory receptors in the nipples transmit signals to the hypothalamus. In response, oxytocin is secreted and released into the bloodstream. Within seconds, cells in the milk ducts contract, ejecting milk into the infant’s mouth. Secondly, in both people, oxytocin is thought to contribute to parent–newborn bonding, known as attachment. Oxytocin is also thought to be involved in feelings of love and closeness, as well as in the sexual response.

### Antidiuretic Hormone (ADH)

The solute concentration of the blood, or blood osmolarity, may change in response to the consumption of certain foods and fluids, as well as in response to disease, injury, medications, or other factors. Blood osmolarity is constantly monitored by **osmoreceptors**—specialized cells within the hypothalamus that are particularly sensitive to the concentration of sodium ions and other solutes.

In response to high blood osmolarity, which can occur during dehydration or following a very salty meal, the osmoreceptors signal the posterior pituitary to release **antidiuretic hormone (ADH)**. The target cells of ADH are located in the tubular cells of the kidneys. Its effect is to increase epithelial permeability to water, allowing increased water reabsorption. The more water reabsorbed from the filtrate, the greater the amount of water that is returned to the blood and the less that is excreted in the urine. A greater concentration of water results in a reduced concentration of solutes. ADH is also known as vasopressin because, in very high concentrations, it causes constriction of blood vessels, which increases blood pressure by increasing peripheral resistance. The release of ADH is controlled by a negative feedback loop. As blood osmolarity decreases, the hypothalamic osmoreceptors sense the change and prompt a corresponding decrease in the secretion of ADH. As a result, less water is reabsorbed from the urine filtrate.

Interestingly, drugs can affect the secretion of ADH. For example, alcohol consumption inhibits the release of ADH, resulting in increased urine production that can eventually lead to dehydration and a hangover. A disease called diabetes insipidus is characterized by chronic underproduction of ADH that causes chronic dehydration. Because little ADH is produced and secreted, not enough water is reabsorbed by the kidneys. Although patients feel thirsty, and increase their fluid consumption, this doesn’t effectively decrease the solute concentration in their blood because ADH levels are not high enough to trigger water reabsorption in the kidneys. Electrolyte imbalances can occur in severe cases of diabetes insipidus.

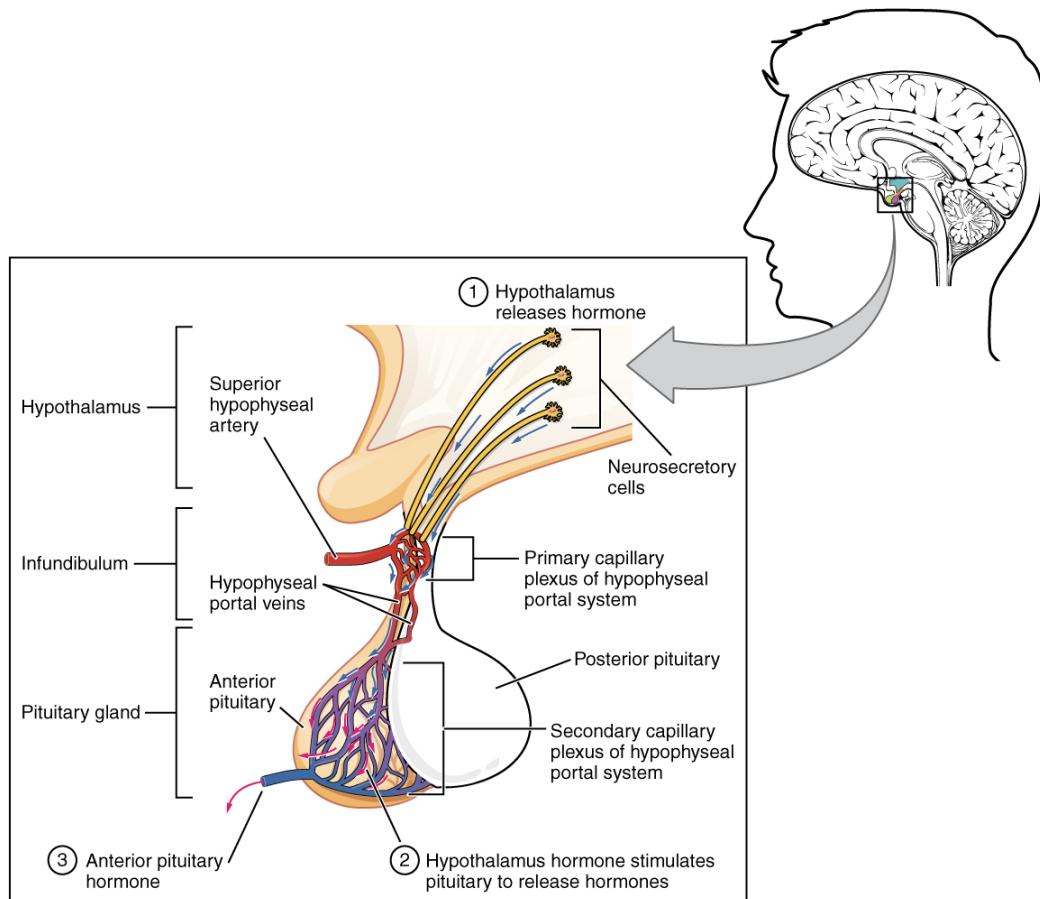
### Anterior Pituitary

The anterior pituitary originates from the digestive tract in the embryo and migrates toward the brain during fetal development. There are three regions: the pars distalis is the most anterior, the pars intermedia is adjacent to the posterior pituitary, and the pars tuberalis is a slender “tube” that wraps the infundibulum.

Recall that the posterior pituitary does not synthesize hormones, but merely stores them. In contrast, the anterior pituitary does manufacture hormones. However, the secretion of hormones from the anterior pituitary is regulated by two classes of hormones. These hormones—secreted by the hypothalamus—are the releasing hormones that stimulate the secretion of hormones from the anterior pituitary and the inhibiting hormones that inhibit secretion.

Hypothalamic hormones are secreted by neurons, but enter the anterior pituitary through blood vessels ([Figure 17.9](#)). Within the infundibulum is a bridge of capillaries that connects the hypothalamus to the anterior pituitary.

This network, called the **hypophyseal portal system**, allows hypothalamic hormones to be transported to the anterior pituitary without first entering the systemic circulation. The system originates from the superior hypophyseal artery, which branches off the carotid arteries and transports blood to the hypothalamus. The branches of the superior hypophyseal artery form the hypophyseal portal system (see [Figure 17.9](#)). Hypothalamic releasing and inhibiting hormones travel through a primary capillary plexus to the portal veins, which carry them into the anterior pituitary. Hormones produced by the anterior pituitary (in response to releasing hormones) enter a secondary capillary plexus, and from there drain into the circulation.

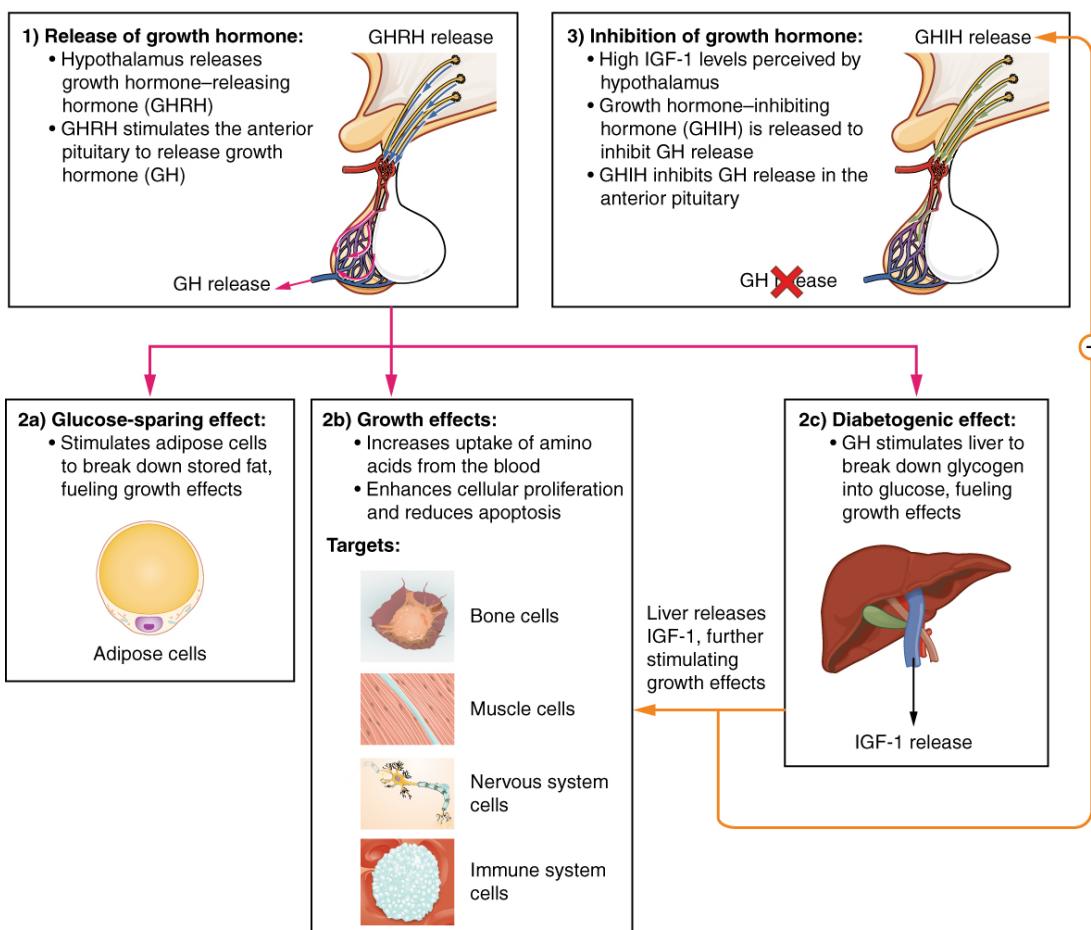


**FIGURE 17.9 Anterior Pituitary** The anterior pituitary manufactures seven hormones. The hypothalamus produces separate hormones that stimulate or inhibit hormone production in the anterior pituitary. Hormones from the hypothalamus reach the anterior pituitary via the hypophyseal portal system.

The anterior pituitary produces seven hormones. These are the growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), beta endorphin, and prolactin. Of the hormones of the anterior pituitary, TSH, ACTH, FSH, and LH are collectively referred to as tropic hormones (*trope-* = “turning”) because they turn on or off the function of other endocrine glands.

#### Growth Hormone

The endocrine system regulates the growth of the human body, protein synthesis, and cellular replication. A major hormone involved in this process is **growth hormone (GH)**, also called somatotropin—a protein hormone produced and secreted by the anterior pituitary gland. Its primary function is anabolic; it promotes protein synthesis and tissue building through direct and indirect mechanisms ([Figure 17.10](#)). GH levels are controlled by the release of GHRH and GHIH (also known as somatostatin) from the hypothalamus.



**FIGURE 17.10 Hormonal Regulation of Growth** Growth hormone (GH) directly accelerates the rate of protein synthesis in skeletal muscle and bones. Insulin-like growth factor 1 (IGF-1) is activated by growth hormone and indirectly supports the formation of new proteins in muscle cells and bone.

A glucose-sparing effect occurs when GH stimulates lipolysis, or the breakdown of adipose tissue, releasing fatty acids into the blood. As a result, many tissues switch from glucose to fatty acids as their main energy source, which means that less glucose is taken up from the bloodstream.

GH also initiates the diabetogenic effect in which GH stimulates the liver to break down glycogen to glucose, which is then deposited into the blood. The name “diabetogenic” is derived from the similarity in elevated blood glucose levels observed between individuals with untreated diabetes mellitus and individuals experiencing GH excess. Blood glucose levels rise as the result of a combination of glucose-sparing and diabetogenic effects.

GH indirectly mediates growth and protein synthesis by triggering the liver and other tissues to produce a group of proteins called **insulin-like growth factors (IGFs)**. These proteins enhance cellular proliferation and inhibit apoptosis, or programmed cell death. IGFs stimulate cells to increase their uptake of amino acids from the blood for protein synthesis. Skeletal muscle and cartilage cells are particularly sensitive to stimulation from IGFs.

Dysfunction of the endocrine system’s control of growth can result in several disorders. For example, **gigantism** is a disorder in children that is caused by the secretion of abnormally large amounts of GH, resulting in excessive growth. A similar condition in adults is **acromegaly**, a disorder that results in the growth of bones in the face, hands, and feet in response to excessive levels of GH in individuals who have stopped growing. Abnormally low levels of GH in children can cause growth impairment—a disorder called **pituitary dwarfism** (also known as growth hormone deficiency).

### Thyroid-Stimulating Hormone

The activity of the thyroid gland is regulated by **thyroid-stimulating hormone (TSH)**, also called thyrotropin. TSH is released from the anterior pituitary in response to thyrotropin-releasing hormone (TRH) from the hypothalamus. As

discussed shortly, it triggers the secretion of thyroid hormones by the thyroid gland. In a classic negative feedback loop, elevated levels of thyroid hormones in the bloodstream then trigger a drop in production of TRH and subsequently TSH.

#### Adrenocorticotrophic Hormone

The **adrenocorticotrophic hormone (ACTH)**, also called corticotropin, stimulates the adrenal cortex (the more superficial “bark” of the adrenal glands) to secrete corticosteroid hormones such as cortisol. ACTH comes from a precursor molecule known as pro-opiomelanocortin (POMC) which produces several biologically active molecules when cleaved, including ACTH, melanocyte-stimulating hormone, and the brain opioid peptides known as endorphins.

The release of ACTH is regulated by the corticotropin-releasing hormone (CRH) from the hypothalamus in response to normal physiologic rhythms. A variety of stressors can also influence its release, and the role of ACTH in the stress response is discussed later in this chapter.

#### Follicle-Stimulating Hormone and Luteinizing Hormone

The endocrine glands secrete a variety of hormones that control the development and regulation of the reproductive system (these glands include the anterior pituitary, the adrenal cortex, and the gonads—the testes and the ovaries). Much of the development of the reproductive system occurs during puberty and is marked by the development of sex-specific characteristics in adolescents. Puberty is initiated by gonadotropin-releasing hormone (GnRH), a hormone produced and secreted by the hypothalamus. GnRH stimulates the anterior pituitary to secrete **gonadotropins**—hormones that regulate the function of the gonads. The levels of GnRH are regulated through a negative feedback loop; high levels of reproductive hormones inhibit the release of GnRH. Throughout life, gonadotropins regulate reproductive function and, in the case of females, the onset and cessation of reproductive capacity.

The gonadotropins include two glycoprotein hormones: **follicle-stimulating hormone (FSH)** stimulates the production and maturation of sex cells, or gametes, including ova and sperm. FSH also promotes follicular growth; these follicles then release estrogens in ovaries. **Luteinizing hormone (LH)** triggers ovulation, as well as the production of estrogens and progesterone by the ovaries. LH stimulates production of testosterone by the testes.

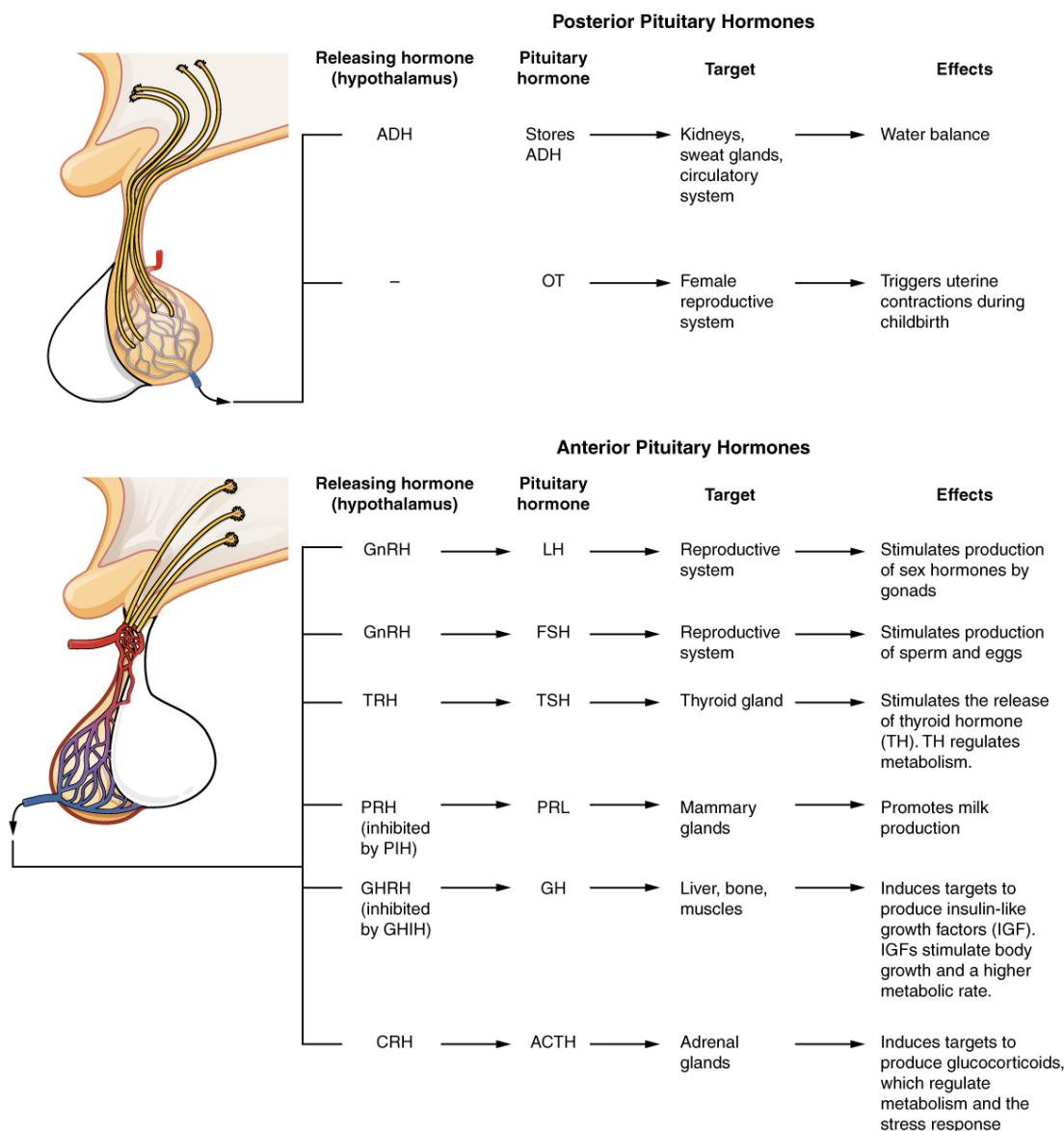
#### Prolactin

As its name implies, **prolactin (PRL)** promotes lactation (milk production). During pregnancy, it contributes to development of the mammary glands, and after birth, it stimulates the mammary glands to produce breast milk. However, the effects of prolactin depend heavily upon the permissive effects of estrogens, progesterone, and other hormones. And as noted earlier, the let-down of milk occurs in response to stimulation from oxytocin.

In non-pregnant females, prolactin secretion is inhibited by prolactin-inhibiting hormone (PIH), which is actually the neurotransmitter dopamine, and is released from neurons in the hypothalamus. Only during pregnancy do prolactin levels rise in response to prolactin-releasing hormone (PRH) from the hypothalamus.

#### Intermediate Pituitary: Melanocyte-Stimulating Hormone

The cells in the zone between the pituitary lobes secrete a hormone known as melanocyte-stimulating hormone (MSH) that is formed by cleavage of the pro-opiomelanocortin (POMC) precursor protein. Local production of MSH in the skin is responsible for melanin production in response to UV light exposure. The role of MSH made by the pituitary is more complicated. For instance, people with lighter skin generally have the same amount of MSH as people with darker skin. Nevertheless, this hormone is capable of darkening of the skin by inducing melanin production in the skin’s melanocytes. People also show increased MSH production during pregnancy; in combination with estrogens, it can lead to darker skin pigmentation, especially the skin of the areolas and labia minora. [Figure 17.11](#) is a summary of the pituitary hormones and their principal effects.



**FIGURE 17.11 Major Pituitary Hormones** Major pituitary hormones and their target organs.

## INTERACTIVE LINK

Visit this [link](http://openstax.org/l/roleofhypo) (<http://openstax.org/l/roleofhypo>) to watch an animation showing the role of the hypothalamus and the pituitary gland. Which hormone is released by the pituitary to stimulate the thyroid gland?

## 17.4 The Thyroid Gland

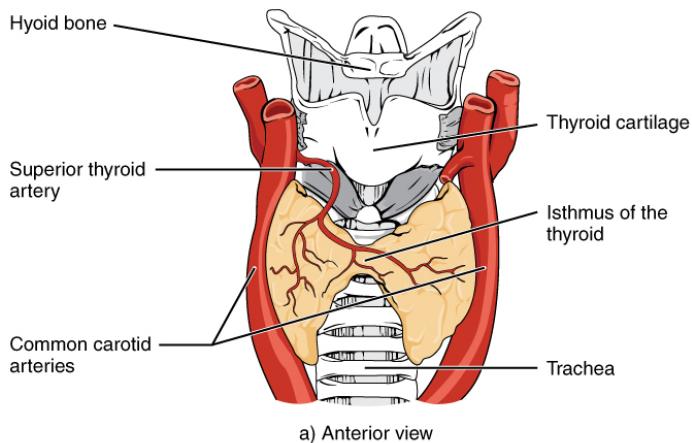
### LEARNING OBJECTIVES

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

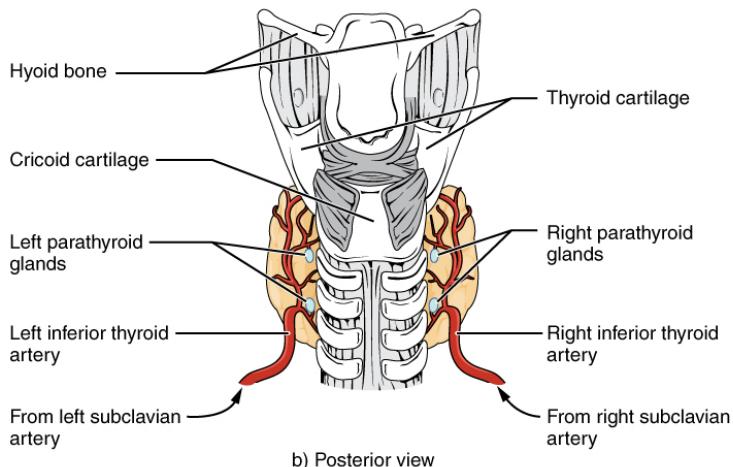
- Describe the location and anatomy of the thyroid gland
- Discuss the synthesis of triiodothyronine and thyroxine
- Explain the role of thyroid hormones in the regulation of basal metabolism
- Identify the hormone produced by the parafollicular cells of the thyroid

A butterfly-shaped organ, the **thyroid gland** is located anterior to the trachea, just inferior to the larynx (Figure 17.12). The medial region, called the isthmus, is flanked by wing-shaped left and right lobes. Each of the thyroid lobes are embedded with parathyroid glands, primarily on their posterior surfaces. The tissue of the thyroid gland is composed mostly of thyroid follicles. The follicles are made up of a central cavity filled with a sticky fluid called

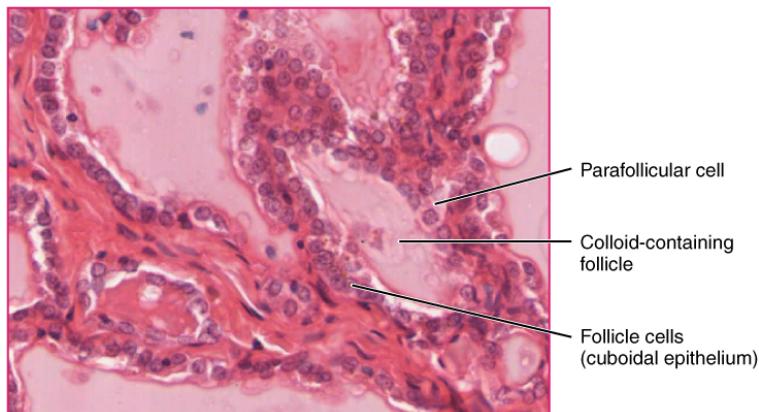
**colloid.** Surrounded by a wall of epithelial follicle cells, the colloid is the center of thyroid hormone production, and that production is dependent on the hormones' essential and unique component: iodine.



a) Anterior view



b) Posterior view



c) Thyroid follicle cells

**FIGURE 17.12 Thyroid Gland** The thyroid gland is located in the neck where it wraps around the trachea. (a) Anterior view of the thyroid gland. (b) Posterior view of the thyroid gland. (c) The glandular tissue is composed primarily of thyroid follicles. The larger parafollicular cells often appear within the matrix of follicle cells. LM  $\times 1332$ . (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

### Synthesis and Release of Thyroid Hormones

Hormones are produced in the colloid when atoms of the mineral iodine attach to a glycoprotein, called thyroglobulin, that is secreted into the colloid by the follicle cells. The following steps outline the hormones'

assembly:

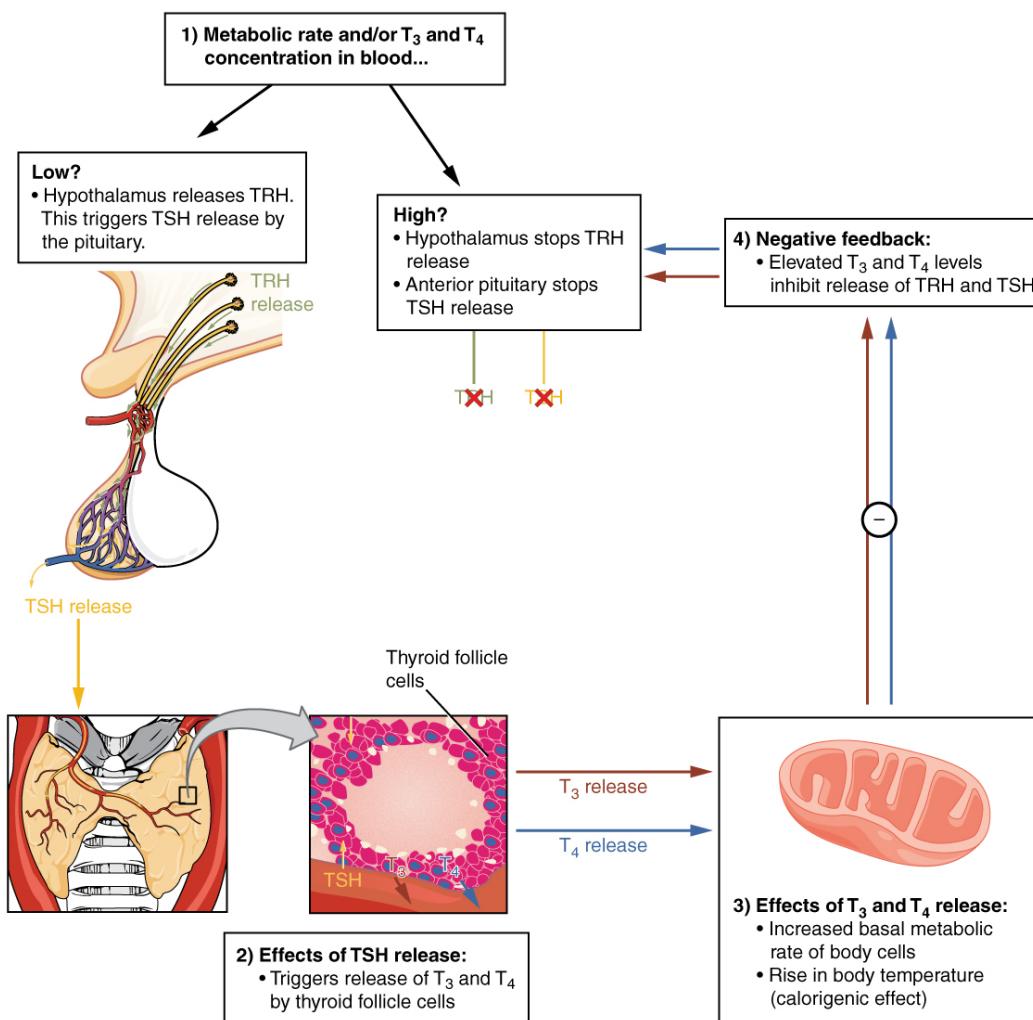
1. Binding of TSH to its receptors in the follicle cells of the thyroid gland causes the cells to actively transport iodide ions ( $I^-$ ) across their cell membrane, from the bloodstream into the cytosol. As a result, the concentration of iodide ions “trapped” in the follicular cells is many times higher than the concentration in the bloodstream.
2. Iodide ions then move to the lumen of the follicle cells that border the colloid. There, the ions undergo oxidation (their negatively charged electrons are removed). The oxidation of two iodide ions ( $2 I^-$ ) results in iodine ( $I_2$ ), which passes through the follicle cell membrane into the colloid.
3. In the colloid, peroxidase enzymes link the iodine to the tyrosine amino acids in thyroglobulin to produce two intermediaries: a tyrosine attached to one iodine and a tyrosine attached to two iodines. When one of each of these intermediaries is linked by covalent bonds, the resulting compound is **triiodothyronine** ( $T_3$ ), a thyroid hormone with three iodines. Much more commonly, two copies of the second intermediary bond, forming tetraiodothyronine, also known as **thyroxine** ( $T_4$ ), a thyroid hormone with four iodines.

These hormones remain in the colloid center of the thyroid follicles until TSH stimulates endocytosis of colloid back into the follicle cells. There, lysosomal enzymes break apart the thyroglobulin colloid, releasing free  $T_3$  and  $T_4$ , which diffuse across the follicle cell membrane and enter the bloodstream.

In the bloodstream, less than one percent of the circulating  $T_3$  and  $T_4$  remains unbound. This free  $T_3$  and  $T_4$  can cross the lipid bilayer of cell membranes and be taken up by cells. The remaining 99 percent of circulating  $T_3$  and  $T_4$  is bound to specialized transport proteins called thyroxine-binding globulins (TBGs), to albumin, or to other plasma proteins. This “packaging” prevents their free diffusion into body cells. When blood levels of  $T_3$  and  $T_4$  begin to decline, bound  $T_3$  and  $T_4$  are released from these plasma proteins and readily cross the membrane of target cells.  $T_3$  is more potent than  $T_4$ , and many cells convert  $T_4$  to  $T_3$  through the removal of an iodine atom.

### Regulation of TH Synthesis

The release of  $T_3$  and  $T_4$  from the thyroid gland is regulated by thyroid-stimulating hormone (TSH). As shown in [Figure 17.13](#), low blood levels of  $T_3$  and  $T_4$  stimulate the release of thyrotropin-releasing hormone (TRH) from the hypothalamus, which triggers secretion of TSH from the anterior pituitary. In turn, TSH stimulates the thyroid gland to secrete  $T_3$  and  $T_4$ . The levels of TRH, TSH,  $T_3$ , and  $T_4$  are regulated by a negative feedback system in which increasing levels of  $T_3$  and  $T_4$  decrease the production and secretion of TSH.



**FIGURE 17.13** Classic Negative Feedback Loop A classic negative feedback loop controls the regulation of thyroid hormone levels.

### Functions of Thyroid Hormones

The thyroid hormones, T<sub>3</sub> and T<sub>4</sub>, are often referred to as metabolic hormones because their levels influence the body's basal metabolic rate, the amount of energy used by the body at rest. When T<sub>3</sub> and T<sub>4</sub> bind to intracellular receptors located on the mitochondria, they cause an increase in nutrient breakdown and the use of oxygen to produce ATP. In addition, T<sub>3</sub> and T<sub>4</sub> initiate the transcription of genes involved in glucose oxidation. Although these mechanisms prompt cells to produce more ATP, the process is inefficient, and an abnormally increased level of heat is released as a byproduct of these reactions. This so-called calorigenic effect (calor- = "heat") raises body temperature.

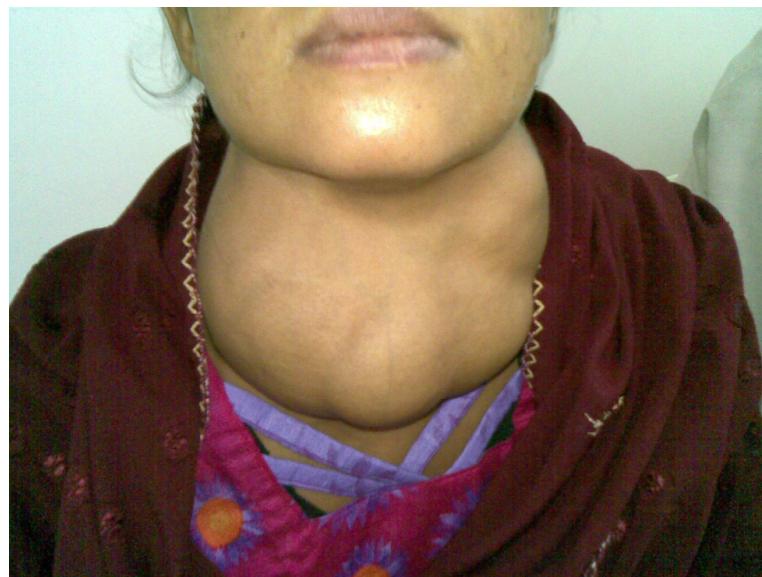
Adequate levels of thyroid hormones are also required for protein synthesis and for fetal and childhood tissue development and growth. They are especially critical for normal development of the nervous system both in utero and in early childhood, and they continue to support neurological function in adults. As noted earlier, these thyroid hormones have a complex interrelationship with reproductive hormones, and deficiencies can influence libido, fertility, and other aspects of reproductive function. Finally, thyroid hormones increase the body's sensitivity to catecholamines (epinephrine and norepinephrine) from the adrenal medulla by upregulation of receptors in the blood vessels. When levels of T<sub>3</sub> and T<sub>4</sub> hormones are excessive, this effect accelerates the heart rate, strengthens the heartbeat, and increases blood pressure. Because thyroid hormones regulate metabolism, heat production, protein synthesis, and many other body functions, thyroid disorders can have severe and widespread consequences.

## Disorders of the...

### Endocrine System: Iodine Deficiency, Hypothyroidism, and Hyperthyroidism

As discussed above, dietary iodine is required for the synthesis of  $T_3$  and  $T_4$ . But for much of the world's population, foods do not provide adequate levels of this mineral, because the amount varies according to the level in the soil in which the food was grown, as well as the irrigation and fertilizers used. Marine fish and shrimp tend to have high levels because they concentrate iodine from seawater, but many people in landlocked regions lack access to seafood. Thus, the primary source of dietary iodine in many countries is iodized salt. Fortification of salt with iodine began in the United States in 1924, and international efforts to iodize salt in the world's poorest nations continue today.

Dietary iodine deficiency can result in the impaired ability to synthesize  $T_3$  and  $T_4$ , leading to a variety of severe disorders. When  $T_3$  and  $T_4$  cannot be produced, TSH is secreted in increasing amounts. As a result of this hyperstimulation, thyroglobulin accumulates in the thyroid gland follicles, increasing their deposits of colloid. The accumulation of colloid increases the overall size of the thyroid gland, a condition called a **goiter** ([Figure 17.14](#)). A goiter is only a visible indication of the deficiency. Other iodine deficiency disorders include impaired growth and development, decreased fertility, and prenatal and infant death. Moreover, iodine deficiency is the primary cause of preventable intellectual disabilities worldwide. **Neonatal hypothyroidism** (cretinism) is characterized by cognitive deficits, short stature, and sometimes deafness and muteness in children and adults born to mothers who were iodine-deficient during pregnancy.



**FIGURE 17.14 Goiter** (credit: "Almazi"/Wikimedia Commons)

In areas of the world with access to iodized salt, dietary deficiency is rare. Instead, inflammation of the thyroid gland is the more common cause of low blood levels of thyroid hormones. Called **hypothyroidism**, the condition is characterized by a low metabolic rate, weight gain, cold extremities, constipation, reduced libido, menstrual irregularities, and reduced mental activity. In contrast, **hyperthyroidism**—an abnormally elevated blood level of thyroid hormones—is often caused by a pituitary or thyroid tumor. In Graves' disease, the hyperthyroid state results from an autoimmune reaction in which antibodies overstimulate the follicle cells of the thyroid gland. Hyperthyroidism can lead to an increased metabolic rate, excessive body heat and sweating, diarrhea, weight loss, tremors, and increased heart rate. The person's eyes may bulge (called exophthalmos) as antibodies produce inflammation in the soft tissues of the orbits. The person may also develop a goiter.

## Calcitonin

The thyroid gland also secretes a hormone called **calcitonin** that is produced by the parafollicular cells (also called C cells) that stud the tissue between distinct follicles. Calcitonin is released in response to a rise in blood calcium

levels. It appears to have a function in decreasing blood calcium concentrations by:

- Inhibiting the activity of osteoclasts, bone cells that release calcium into the circulation by degrading bone matrix
- Increasing osteoblastic activity
- Decreasing calcium absorption in the intestines
- Increasing calcium loss in the urine

However, these functions are usually not significant in maintaining calcium homeostasis, so the importance of calcitonin is not entirely understood. Pharmaceutical preparations of calcitonin are sometimes prescribed to reduce osteoclast activity in people with osteoporosis and to reduce the degradation of cartilage in people with osteoarthritis. The hormones secreted by thyroid are summarized in [Table 17.4](#).

**Thyroid Hormones**

Associated hormones	Chemical class	Effect
Thyroxine ( $T_4$ ), triiodothyronine ( $T_3$ )	Amine	Stimulate basal metabolic rate
Calcitonin	Peptide	Reduces blood $\text{Ca}^{2+}$ levels

**TABLE 17.4**

Of course, calcium is critical for many other biological processes. It is a second messenger in many signaling pathways, and is essential for muscle contraction, nerve impulse transmission, and blood clotting. Given these roles, it is not surprising that blood calcium levels are tightly regulated by the endocrine system. The organs involved in the regulation are the parathyroid glands.

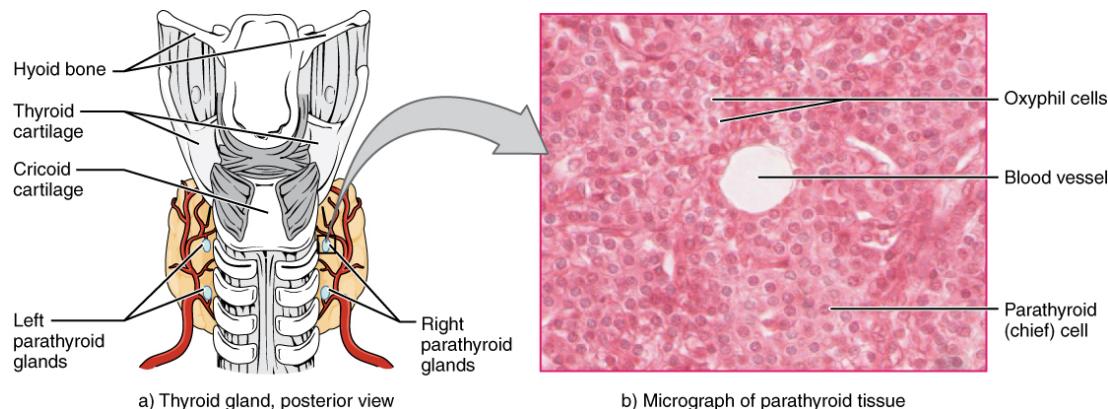
## 17.5 The Parathyroid Glands

### LEARNING OBJECTIVES

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

- Describe the location and structure of the parathyroid glands
- Describe the hormonal control of blood calcium levels
- Discuss the physiological response of parathyroid dysfunction

The **parathyroid glands** are tiny, round structures usually found embedded in the posterior surface of the thyroid gland ([Figure 17.15](#)). A thick connective tissue capsule separates the glands from the thyroid tissue. Most people have four parathyroid glands, but occasionally there are more in tissues of the neck or chest. The function of one type of parathyroid cells, the oxyphil cells, is not clear. The primary functional cells of the parathyroid glands are the chief cells. These epithelial cells produce and secrete the **parathyroid hormone (PTH)**, the major hormone involved in the regulation of blood calcium levels.



**FIGURE 17.15 Parathyroid Glands** The small parathyroid glands are embedded in the posterior surface of the thyroid gland. LM  $\times 760$ .

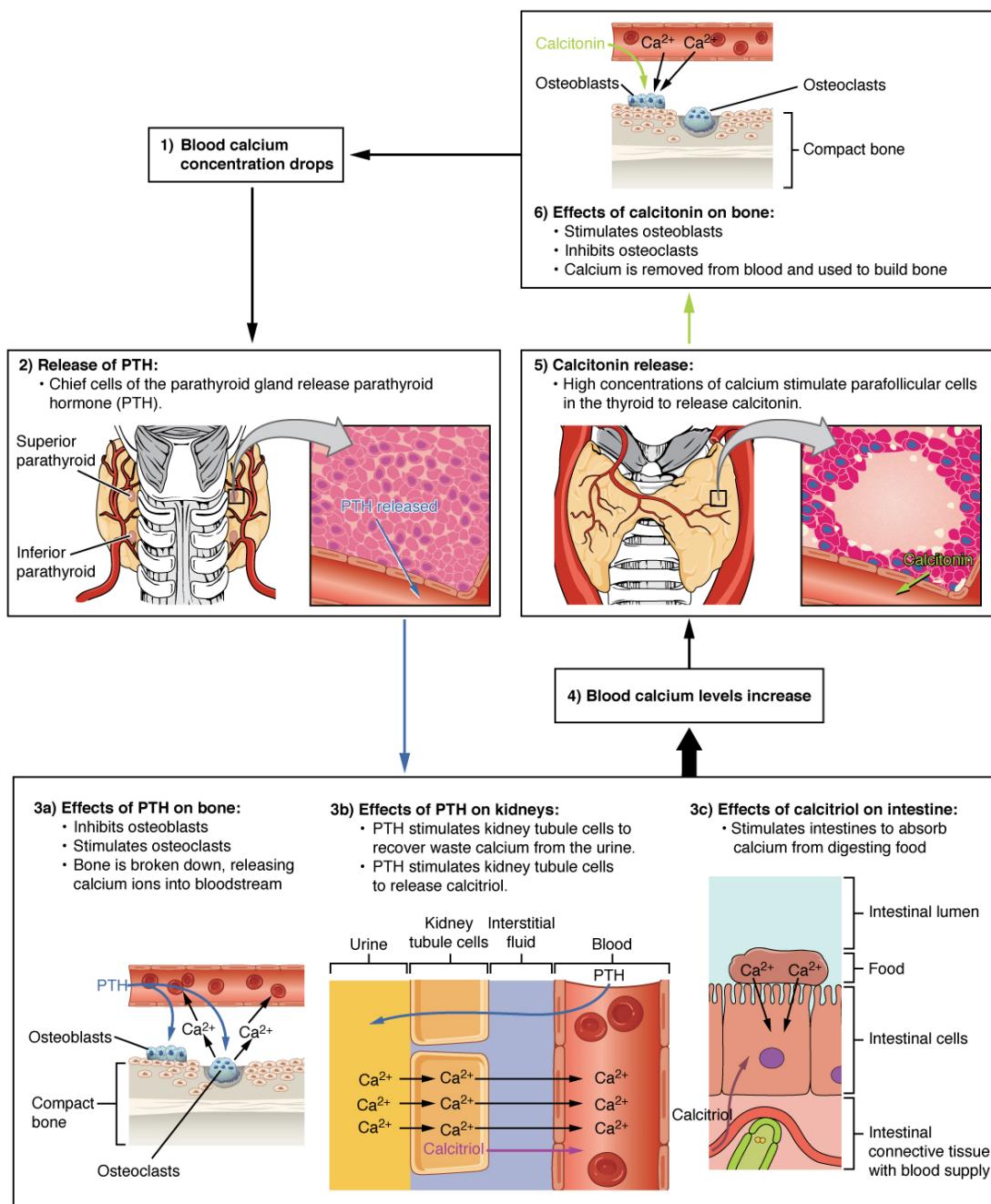
(Micrograph provided by the Regents of University of Michigan Medical School © 2012)

### **INTERACTIVE LINK**

View the [University of Michigan WebScope](http://openstax.org/l/parathyroid) (<http://openstax.org/l/parathyroid>) to explore the tissue sample in greater detail.

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The parathyroid glands produce and secrete PTH, a peptide hormone, in response to low blood calcium levels ([Figure 17.16](#)). PTH secretion causes the release of calcium from the bones by stimulating osteoclasts, which secrete enzymes that degrade bone and release calcium into the interstitial fluid. PTH also inhibits osteoblasts, the cells involved in bone deposition, thereby sparing blood calcium. PTH causes increased reabsorption of calcium (and magnesium) in the kidney tubules from the urine filtrate. In addition, PTH initiates the production of the steroid hormone calcitriol (also known as 1,25-dihydroxyvitamin D), which is the active form of vitamin D<sub>3</sub>, in the kidneys. Calcitriol then stimulates increased absorption of dietary calcium by the intestines. A negative feedback loop regulates the levels of PTH, with rising blood calcium levels inhibiting further release of PTH.



**FIGURE 17.16 Parathyroid Hormone in Maintaining Blood Calcium Homeostasis** Parathyroid hormone increases blood calcium levels when they drop too low. Conversely, calcitonin, which is released from the thyroid gland, decreases blood calcium levels when they become too high. These two mechanisms constantly maintain blood calcium concentration at homeostasis.

Abnormally high activity of the parathyroid gland can cause **hyperparathyroidism**, a disorder caused by an overproduction of PTH that results in excessive calcium reabsorption from bone. Hyperparathyroidism can significantly decrease bone density, leading to spontaneous fractures or deformities. As blood calcium levels rise, cell membrane permeability to sodium is decreased, and the responsiveness of the nervous system is reduced. At the same time, calcium deposits may collect in the body's tissues and organs, impairing their functioning.

In contrast, abnormally low blood calcium levels may be caused by parathyroid hormone deficiency, called **hypoparathyroidism**, which may develop following injury or surgery involving the thyroid gland. Low blood calcium increases membrane permeability to sodium, resulting in muscle twitching, cramping, spasms, or convulsions. Severe deficits can paralyze muscles, including those involved in breathing, and can be fatal.

When blood calcium levels are high, calcitonin is produced and secreted by the parafollicular cells of the thyroid

gland. As discussed earlier, calcitonin inhibits the activity of osteoclasts, reduces the absorption of dietary calcium in the intestine, and signals the kidneys to reabsorb less calcium, resulting in larger amounts of calcium excreted in the urine.

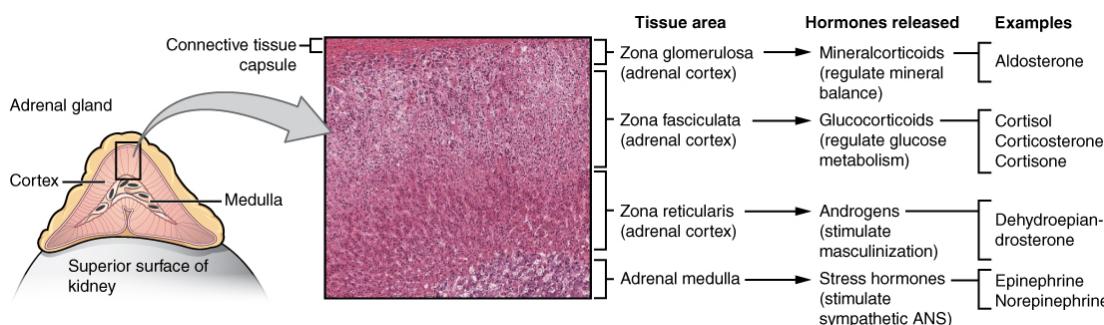
## 17.6 The Adrenal Glands

### LEARNING OBJECTIVES

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

- Describe the location and structure of the adrenal glands
- Identify the hormones produced by the adrenal cortex and adrenal medulla, and summarize their target cells and effects

The **adrenal glands** are wedges of glandular and neuroendocrine tissue adhering to the top of the kidneys by a fibrous capsule (Figure 17.17). The adrenal glands have a rich blood supply and experience one of the highest rates of blood flow in the body. They are served by several arteries branching off the aorta, including the suprarenal and renal arteries. Blood flows to each adrenal gland at the adrenal cortex and then drains into the adrenal medulla. Adrenal hormones are released into the circulation via the left and right suprarenal veins.



**FIGURE 17.17 Adrenal Glands** Both adrenal glands sit atop the kidneys and are composed of an outer cortex and an inner medulla, all surrounded by a connective tissue capsule. The cortex can be subdivided into additional zones, all of which produce different types of hormones. LM  $\times$  204. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

### INTERACTIVE LINK

View the [University of Michigan WebScope](http://openstax.org/l/adrenal) (<http://openstax.org/l/adrenal>) to explore the tissue sample in greater detail.

The adrenal gland consists of an outer cortex of glandular tissue and an inner medulla of nervous tissue. The cortex itself is divided into three zones: the **zona glomerulosa**, the **zona fasciculata**, and the **zona reticularis**. Each region secretes its own set of hormones.

The **adrenal cortex**, as a component of the hypothalamic-pituitary-adrenal (HPA) axis, secretes steroid hormones important for the regulation of the long-term stress response, blood pressure and blood volume, nutrient uptake and storage, fluid and electrolyte balance, and inflammation. The HPA axis involves the stimulation of hormone release of adrenocorticotropic hormone (ACTH) from the pituitary by the hypothalamus. ACTH then stimulates the adrenal cortex to produce the hormone cortisol. This pathway will be discussed in more detail below.

The **adrenal medulla** is neuroendocrine tissue composed of postganglionic sympathetic nervous system (SNS) neurons. It is really an extension of the autonomic nervous system, which regulates homeostasis in the body. The sympathomedullary (SAM) pathway involves the stimulation of the medulla by impulses from the hypothalamus via neurons from the thoracic spinal cord. The medulla is stimulated to secrete the amine hormones epinephrine and norepinephrine.

One of the major functions of the adrenal gland is to respond to stress. Stress can be either physical or psychological or both. Physical stresses include exposing the body to injury, walking outside in cold and wet conditions without a coat on, or malnutrition. Psychological stresses include the perception of a physical threat, a fight with a loved one, or just a bad day at school.

The body responds in different ways to short-term stress and long-term stress following a pattern known as the

**general adaptation syndrome (GAS).** Stage one of GAS is called the **alarm reaction**. This is short-term stress, the fight-or-flight response, mediated by the hormones epinephrine and norepinephrine from the adrenal medulla via the SAM pathway. Their function is to prepare the body for extreme physical exertion. Once this stress is relieved, the body quickly returns to normal. The section on the adrenal medulla covers this response in more detail.

If the stress is not soon relieved, the body adapts to the stress in the second stage called the **stage of resistance**. If a person is starving for example, the body may send signals to the gastrointestinal tract to maximize the absorption of nutrients from food.

If the stress continues for a longer term however, the body responds with symptoms quite different than the fight-or-flight response. During the **stage of exhaustion**, individuals may begin to suffer depression, the suppression of their immune response, severe fatigue, or even a fatal heart attack. These symptoms are mediated by the hormones of the adrenal cortex, especially cortisol, released as a result of signals from the HPA axis.

Adrenal hormones also have several non-stress-related functions, including the increase of blood sodium and glucose levels, which will be described in detail below.

### Adrenal Cortex

The adrenal cortex consists of multiple layers of lipid-storing cells that occur in three structurally distinct regions. Each of these regions produces different hormones.

#### INTERACTIVE LINK

Visit this [link](http://openstax.org/l/adrenalglands) (<http://openstax.org/l/adrenalglands>) to view an animation describing the location and function of the adrenal glands. Which hormone produced by the adrenal glands is responsible for the mobilization of energy stores?

#### Hormones of the Zona Glomerulosa

The most superficial region of the adrenal cortex is the zona glomerulosa, which produces a group of hormones collectively referred to as **mineralocorticoids** because of their effect on body minerals, especially sodium and potassium. These hormones are essential for fluid and electrolyte balance.

**Aldosterone** is the major mineralocorticoid. It is important in the regulation of the concentration of sodium and potassium ions in urine, sweat, and saliva. For example, it is released in response to elevated blood  $K^+$ , low blood  $Na^+$ , low blood pressure, or low blood volume. In response, aldosterone increases the excretion of  $K^+$  and the retention of  $Na^+$ , which in turn increases blood volume and blood pressure. Its secretion is prompted when CRH from the hypothalamus triggers ACTH release from the anterior pituitary.

Aldosterone is also a key component of the renin-angiotensin-aldosterone system (RAAS) in which specialized cells of the kidneys secrete the enzyme renin in response to low blood volume or low blood pressure. Renin then catalyzes the conversion of the blood protein angiotensinogen, produced by the liver, to the hormone angiotensin I. Angiotensin I is converted in the lungs to angiotensin II by **angiotensin-converting enzyme** (ACE). Angiotensin II has three major functions:

1. Initiating vasoconstriction of the arterioles, decreasing blood flow
2. Stimulating kidney tubules to reabsorb  $NaCl$  and water, increasing blood volume
3. Signaling the adrenal cortex to secrete aldosterone, the effects of which further contribute to fluid retention, restoring blood pressure and blood volume

For individuals with hypertension, or high blood pressure, drugs are available that block the production of angiotensin II. These drugs, known as ACE inhibitors, block the ACE enzyme from converting angiotensin I to angiotensin II, thus mitigating the latter's ability to increase blood pressure.

#### Hormones of the Zona Fasciculata

The intermediate region of the adrenal cortex is the zona fasciculata, named as such because the cells form small fascicles (bundles) separated by tiny blood vessels. The cells of the zona fasciculata produce hormones called **glucocorticoids** because of their role in glucose metabolism. The most important of these is **cortisol**, some of which the liver converts to cortisone. A glucocorticoid produced in much smaller amounts is corticosterone. In response to long-term stressors, the hypothalamus secretes CRH, which in turn triggers the release of ACTH by the anterior

pituitary. ACTH triggers the release of the glucocorticoids. Their overall effect is to inhibit tissue building while stimulating the breakdown of stored nutrients to maintain adequate fuel supplies. In conditions of long-term stress, for example, cortisol promotes the catabolism of glycogen to glucose, the catabolism of stored triglycerides into fatty acids and glycerol, and the catabolism of muscle proteins into amino acids. These raw materials can then be used to synthesize additional glucose and ketones for use as body fuels. The hippocampus, which is part of the temporal lobe of the cerebral cortices and important in memory formation, is highly sensitive to stress levels because of its many glucocorticoid receptors.

You are probably familiar with prescription and over-the-counter medications containing glucocorticoids, such as cortisone injections into inflamed joints, prednisone tablets and steroid-based inhalers used to manage severe asthma, and hydrocortisone creams applied to relieve itchy rashes. These drugs reflect another role of cortisol—the downregulation of the immune system, which inhibits the inflammatory response.

#### Hormones of the Zona Reticularis

The deepest region of the adrenal cortex is the zona reticularis, which produces small amounts of a class of steroid sex hormones called androgens. During puberty and most of adulthood, androgens are produced in the gonads. The androgens produced in the zona reticularis supplement the gonadal androgens. They are produced in response to ACTH from the anterior pituitary and are converted in the tissues to testosterone or estrogens. In adult females, they may contribute to the sex drive, but their function in adult males is not well understood. In post-menopausal people, as the functions of the ovaries decline, the main source of estrogens becomes the androgens produced by the zona reticularis.

#### Adrenal Medulla

As noted earlier, the adrenal cortex releases glucocorticoids in response to long-term stress such as severe illness. In contrast, the adrenal medulla releases its hormones in response to acute, short-term stress mediated by the sympathetic nervous system (SNS).

The medullary tissue is composed of unique postganglionic SNS neurons called **chromaffin** cells, which are large and irregularly shaped, and produce the neurotransmitters **epinephrine** (also called adrenaline) and **norepinephrine** (or noradrenaline). Epinephrine is produced in greater quantities—approximately a 4 to 1 ratio with norepinephrine—and is the more powerful hormone. Because the chromaffin cells release epinephrine and norepinephrine into the systemic circulation, where they travel widely and exert effects on distant cells, they are considered hormones. Derived from the amino acid tyrosine, they are chemically classified as catecholamines.

The secretion of medullary epinephrine and norepinephrine is controlled by a neural pathway that originates from the hypothalamus in response to danger or stress (the SAM pathway). Both epinephrine and norepinephrine signal the liver and skeletal muscle cells to convert glycogen into glucose, resulting in increased blood glucose levels. These hormones increase the heart rate, pulse, and blood pressure to prepare the body to fight the perceived threat or flee from it. In addition, the pathway dilates the airways, raising blood oxygen levels. It also prompts vasodilation, further increasing the oxygenation of important organs such as the lungs, brain, heart, and skeletal muscle. At the same time, it triggers vasoconstriction to blood vessels serving less essential organs such as the gastrointestinal tract, kidneys, and skin, and downregulates some components of the immune system. Other effects include a dry mouth, loss of appetite, pupil dilation, and a loss of peripheral vision. The major hormones of the adrenal glands are summarized in [Table 17.5](#).

### Hormones of the Adrenal Glands

Adrenal gland	Associated hormones	Chemical class	Effect
Adrenal cortex	Aldosterone	Steroid	Increases blood Na <sup>+</sup> levels
Adrenal cortex	Cortisol, corticosterone, cortisone	Steroid	Increase blood glucose levels
Adrenal medulla	Epinephrine, norepinephrine	Amine	Stimulate fight-or-flight response

**TABLE 17.5**

### Disorders Involving the Adrenal Glands

Several disorders are caused by the dysregulation of the hormones produced by the adrenal glands. For example, Cushing's disease is a disorder characterized by high blood glucose levels and the accumulation of lipid deposits on the face and neck. It is caused by hypersecretion of cortisol. The most common source of Cushing's disease is a pituitary tumor that secretes cortisol or ACTH in abnormally high amounts. Other common signs of Cushing's disease include the development of a moon-shaped face, a buffalo hump on the back of the neck, rapid weight gain, and hair loss. Chronically elevated glucose levels are also associated with an elevated risk of developing type 2 diabetes. In addition to hyperglycemia, chronically elevated glucocorticoids compromise immunity, resistance to infection, and memory, and can result in rapid weight gain and hair loss.

In contrast, the hyposecretion of corticosteroids can result in Addison's disease, a rare disorder that causes low blood glucose levels and low blood sodium levels. The signs and symptoms of Addison's disease are vague and are typical of other disorders as well, making diagnosis difficult. They may include general weakness, abdominal pain, weight loss, nausea, vomiting, sweating, and cravings for salty food.

## 17.7 The Pineal Gland

### LEARNING OBJECTIVES

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

- Describe the location and structure of the pineal gland
- Discuss the function of melatonin

Recall that the hypothalamus, part of the diencephalon of the brain, sits inferior and somewhat anterior to the thalamus. Inferior but somewhat posterior to the thalamus is the **pineal gland**, a tiny endocrine gland whose functions are not entirely clear. The **pinealocyte** cells that make up the pineal gland are known to produce and secrete the amine hormone **melatonin**, which is derived from serotonin.

The secretion of melatonin varies according to the level of light received from the environment. When photons of light stimulate the retinas of the eyes, a nerve impulse is sent to a region of the hypothalamus called the suprachiasmatic nucleus (SCN), which is important in regulating biological rhythms. From the SCN, the nerve signal is carried to the spinal cord and eventually to the pineal gland, where the production of melatonin is inhibited. As a result, blood levels of melatonin fall, promoting wakefulness. In contrast, as light levels decline—such as during the evening—melatonin production increases, boosting blood levels and causing drowsiness.

### INTERACTIVE LINK

Visit this [link](http://openstax.org/l/melatonin) (<http://openstax.org/l/melatonin>) to view an animation describing the function of the hormone melatonin. What should you avoid doing in the middle of your sleep cycle that would lower melatonin?

The secretion of melatonin may influence the body's circadian rhythms, the dark-light fluctuations that affect not only sleepiness and wakefulness, but also appetite and body temperature. Interestingly, children have higher melatonin levels than adults, which may prevent the release of gonadotropins from the anterior pituitary, thereby inhibiting the onset of puberty. Finally, an antioxidant role of melatonin is the subject of current research.

Jet lag occurs when a person travels across several time zones and feels sleepy during the day or wakeful at night. Traveling across multiple time zones significantly disturbs the light-dark cycle regulated by melatonin. It can take up to several days for melatonin synthesis to adjust to the light-dark patterns in the new environment, resulting in jet lag. Some air travelers take melatonin supplements to induce sleep.

## 17.8 Gonadal and Placental Hormones

### LEARNING OBJECTIVES

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

- Identify the most important hormones produced by the testes and ovaries
- Name the hormones produced by the placenta and state their functions

This section briefly discusses the hormonal role of the gonads—the testes and ovaries—which produce the sex cells (sperm and ova) and secrete the gonadal hormones. The roles of the gonadotropins released from the anterior pituitary (FSH and LH) were discussed earlier.

The primary hormone produced by the testes is **testosterone**, a steroid hormone important in the development of the testicular reproductive system, the maturation of sperm cells, and the development of secondary sex characteristics such as a deepened voice, body hair, and increased muscle mass. Interestingly, testosterone is also produced in the ovaries, but at a much reduced level. In addition, the testes produce the peptide hormone **inhibin**, which inhibits the secretion of FSH from the anterior pituitary gland. FSH stimulates spermatogenesis.

The primary hormones produced by the ovaries are **estrogens**, which include estradiol, estriol, and estrone. Estrogens play an important role in a larger number of physiological processes, including the development of the ovarian reproductive system, regulation of the menstrual cycle, the development of secondary sex characteristics such as increased adipose tissue and the development of breast tissue, and the maintenance of pregnancy. Another significant ovarian hormone is **progesterone**, which contributes to regulation of the menstrual cycle and is important in preparing the body for pregnancy as well as maintaining pregnancy. In addition, the granulosa cells of the ovarian follicles produce inhibin, which inhibits the secretion of FSH. During the initial stages of pregnancy, an organ called the placenta develops within the uterus. The placenta supplies oxygen and nutrients to the fetus, excretes waste products, and produces and secretes estrogens and progesterone. The placenta produces human chorionic gonadotropin (hCG) as well. The hCG hormone promotes progesterone synthesis and reduces the mother's immune function to protect the fetus from immune rejection. It also secretes human placental lactogen (hPL), which plays a role in preparing the breasts for lactation, and relaxin, which is thought to help soften and widen the pubic symphysis in preparation for childbirth. The hormones controlling reproduction are summarized in [Table 17.6](#).

**Reproductive Hormones**

Gonad	Associated hormones	Chemical class	Effect
Testes	Testosterone	Steroid	Stimulates development of secondary sex characteristics and sperm production
Testes	Inhibin	Protein	Inhibits FSH release from pituitary
Ovaries	Estrogens and progesterone	Steroid	Stimulate development of secondary sex characteristics and prepare the body for childbirth
Placenta	Human chorionic gonadotropin	Protein	Promotes progesterone synthesis during pregnancy and inhibits immune response against fetus

**TABLE 17.6**

## Everyday Connection

### Anabolic Steroids

The endocrine system can be exploited for illegal or unethical purposes. A prominent example of this is the use of steroid drugs by professional athletes.

Commonly used for performance enhancement, anabolic steroids are synthetic versions of the sex hormone, testosterone. By boosting natural levels of this hormone, athletes experience increased muscle mass. Synthetic versions of human growth hormone are also used to build muscle mass.

The use of performance-enhancing drugs is banned by all major collegiate and professional sports organizations in the United States because they impart an unfair advantage to athletes who take them. In addition, the drugs can cause significant and dangerous side effects. For example, anabolic steroid use can increase cholesterol levels, raise blood pressure, and damage the liver. Altered testosterone levels (both too low or too high) have been implicated in causing structural damage to the heart, and increasing the risk for cardiac arrhythmias, heart attacks, congestive heart failure, and sudden death. Paradoxically, steroids can have effects, including shriveled testicles and enlarged breast tissue. In females, their use can cause effects such as an enlarged clitoris and growth of facial hair. In all people, their use can promote increased aggression (commonly known as “roid-rage”), depression, sleep disturbances, severe acne, and infertility.

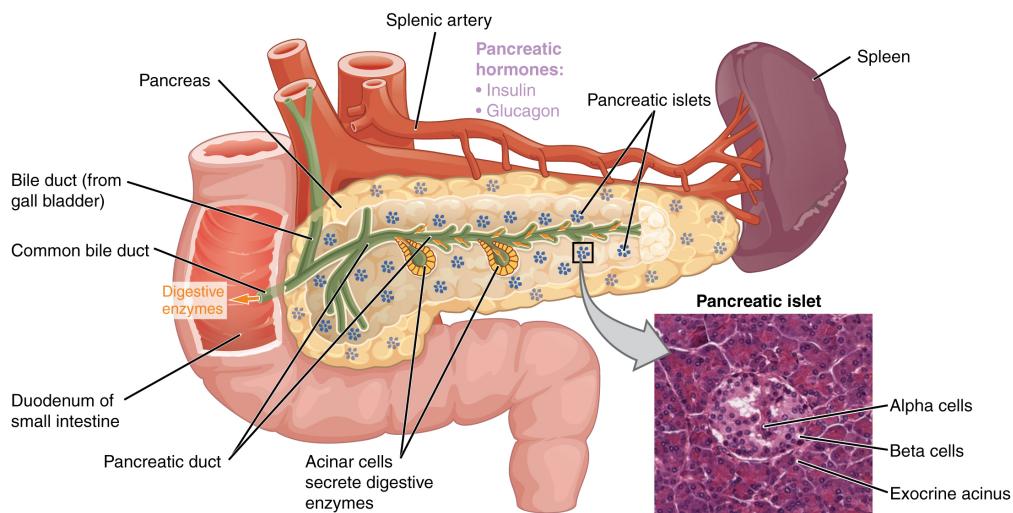
## 17.9 The Endocrine Pancreas

### LEARNING OBJECTIVES

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

- Describe the location and structure of the pancreas, and the morphology and function of the pancreatic islets
- Compare and contrast the functions of insulin and glucagon

The **pancreas** is a long, slender organ, most of which is located posterior to the bottom half of the stomach ([Figure 17.18](#)). Although it is primarily an exocrine gland, secreting a variety of digestive enzymes, the pancreas has an endocrine function. Its **pancreatic islets**—clusters of cells formerly known as the islets of Langerhans—secrete the hormones glucagon, insulin, somatostatin, and pancreatic polypeptide (PP).



**FIGURE 17.18 Pancreas** The pancreatic exocrine function involves the acinar cells secreting digestive enzymes that are transported into the small intestine by the pancreatic duct. Its endocrine function involves the secretion of insulin (produced by beta cells) and glucagon (produced by alpha cells) within the pancreatic islets. These two hormones regulate the rate of glucose metabolism in the body. The micrograph reveals pancreatic islets. LM  $\times 760$ . (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

### INTERACTIVE LINK

View the [University of Michigan WebScope](http://openstax.org/l/pancreaticislet) (<http://openstax.org/l/pancreaticislet>) to explore the tissue sample in greater detail.

## Cells and Secretions of the Pancreatic Islets

The pancreatic islets each contain four varieties of cells:

- The **alpha cell** produces the hormone glucagon and makes up approximately 20 percent of each islet. Glucagon plays an important role in blood glucose regulation; low blood glucose levels stimulate its release.
- The **beta cell** produces the hormone insulin and makes up approximately 75 percent of each islet. Elevated blood glucose levels stimulate the release of insulin.
- The **delta cell** accounts for four percent of the islet cells and secretes the peptide hormone somatostatin. Recall that somatostatin is also released by the hypothalamus (as GHIH), and the stomach and intestines also secrete it. An inhibiting hormone, pancreatic somatostatin inhibits the release of both glucagon and insulin.
- The **PP cell** accounts for about one percent of islet cells and secretes the pancreatic polypeptide hormone. It is thought to play a role in appetite, as well as in the regulation of pancreatic exocrine and endocrine secretions. Pancreatic polypeptide released following a meal may reduce further food consumption; however, it is also released in response to fasting.

## Regulation of Blood Glucose Levels by Insulin and Glucagon

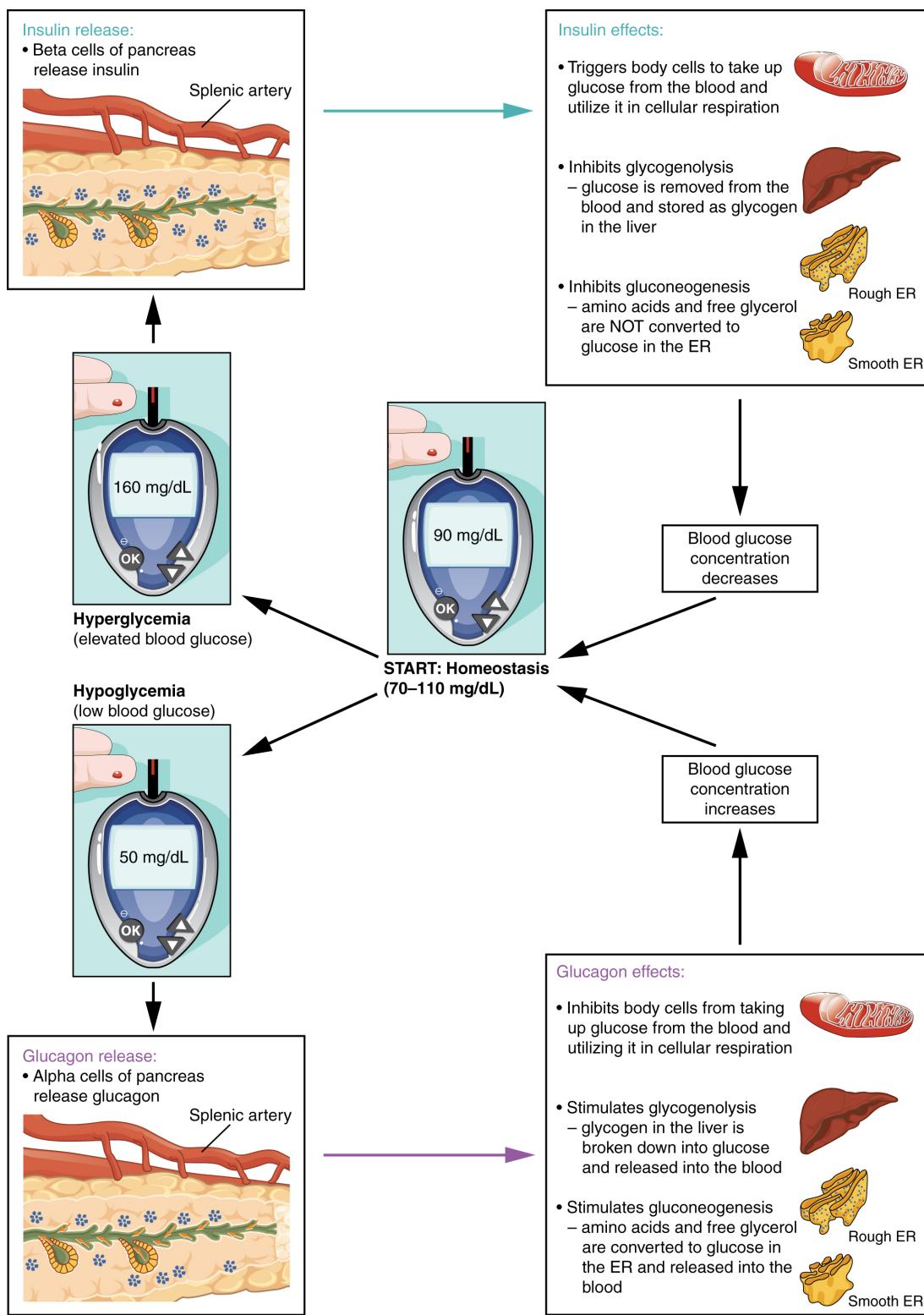
Glucose is required for cellular respiration and is the preferred fuel for all body cells. The body derives glucose from the breakdown of the carbohydrate-containing foods and drinks we consume. Glucose not immediately taken up by cells for fuel can be stored by the liver and muscles as glycogen, or converted to triglycerides and stored in the adipose tissue. Hormones regulate both the storage and the utilization of glucose as required. Receptors located in the pancreas sense blood glucose levels, and subsequently the pancreatic cells secrete glucagon or insulin to maintain normal levels.

### Glucagon

Receptors in the pancreas can sense the decline in blood glucose levels, such as during periods of fasting or during prolonged labor or exercise ([Figure 17.19](#)). In response, the alpha cells of the pancreas secrete the hormone **glucagon**, which has several effects:

- It stimulates the liver to convert its stores of glycogen back into glucose. This response is known as glycogenolysis. The glucose is then released into the circulation for use by body cells.
- It stimulates the liver to take up amino acids from the blood and convert them into glucose. This response is known as gluconeogenesis.
- It stimulates lipolysis, the breakdown of stored triglycerides into free fatty acids and glycerol. Some of the free glycerol released into the bloodstream travels to the liver, which converts it into glucose. This is also a form of gluconeogenesis.

Taken together, these actions increase blood glucose levels. The activity of glucagon is regulated through a negative feedback mechanism; rising blood glucose levels inhibit further glucagon production and secretion.



**FIGURE 17.19 Homeostatic Regulation of Blood Glucose Levels** Blood glucose concentration is tightly maintained between 70 mg/dL and 110 mg/dL. If blood glucose concentration rises above this range, insulin is released, which stimulates body cells to remove glucose from the blood. If blood glucose concentration drops below this range, glucagon is released, which stimulates body cells to release glucose into the blood.

### Insulin

The primary function of **insulin** is to facilitate the uptake of glucose into body cells. Red blood cells, as well as cells of the brain, liver, kidneys, and the lining of the small intestine, do not have insulin receptors on their cell membranes and do not require insulin for glucose uptake. Although all other body cells do require insulin if they are

to take glucose from the bloodstream, skeletal muscle cells and adipose cells are the primary targets of insulin.

The presence of food in the intestine triggers the release of gastrointestinal tract hormones such as glucose-dependent insulinotropic peptide (previously known as gastric inhibitory peptide). This is in turn the initial trigger for insulin production and secretion by the beta cells of the pancreas. Once nutrient absorption occurs, the resulting surge in blood glucose levels further stimulates insulin secretion.

Precisely how insulin facilitates glucose uptake is not entirely clear. However, insulin appears to activate a tyrosine kinase receptor, triggering the phosphorylation of many substrates within the cell. These multiple biochemical reactions converge to support the movement of intracellular vesicles containing facilitative glucose transporters to the cell membrane. In the absence of insulin, these transport proteins are normally recycled slowly between the cell membrane and cell interior. Insulin triggers the rapid movement of a pool of glucose transporter vesicles to the cell membrane, where they fuse and expose the glucose transporters to the extracellular fluid. The transporters then move glucose by facilitated diffusion into the cell interior.

### INTERACTIVE LINK

Visit this [link](http://openstax.org/l/pancreas1) (<http://openstax.org/l/pancreas1>) to view an animation describing the location and function of the pancreas. What goes wrong in the function of insulin in type 2 diabetes?

Insulin also reduces blood glucose levels by stimulating glycolysis, the metabolism of glucose for generation of ATP. Moreover, it stimulates the liver to convert excess glucose into glycogen for storage, and it inhibits enzymes involved in glycogenolysis and gluconeogenesis. Finally, insulin promotes triglyceride and protein synthesis. The secretion of insulin is regulated through a negative feedback mechanism. As blood glucose levels decrease, further insulin release is inhibited. The pancreatic hormones are summarized in [Table 17.7](#).

Hormones of the Pancreas

Associated hormones	Chemical class	Effect
Insulin (beta cells)	Protein	Reduces blood glucose levels
Glucagon (alpha cells)	Protein	Increases blood glucose levels
Somatostatin (delta cells)	Protein	Inhibits insulin and glucagon release
Pancreatic polypeptide (PP cells)	Protein	Role in appetite

TABLE 17.7

### Disorders of the...

#### Endocrine System: Diabetes Mellitus

Dysfunction of insulin production and secretion, as well as the target cells' responsiveness to insulin, can lead to a condition called **diabetes mellitus**. An increasingly common disease, diabetes mellitus has been diagnosed in more than 18 million adults in the United States, and more than 200,000 children. It is estimated that up to 7 million more adults have the condition but have not been diagnosed. In addition, approximately 79 million people in the US are estimated to have pre-diabetes, a condition in which blood glucose levels are abnormally high, but not yet high enough to be classified as diabetes.

There are two main forms of diabetes mellitus. Type 1 diabetes is an autoimmune disease affecting the beta cells of the pancreas. Certain genes are recognized to increase susceptibility. The beta cells of people with type 1 diabetes do not produce insulin; thus, synthetic insulin must be administered by injection or infusion. This form of diabetes accounts for less than five percent of all diabetes cases.

Type 2 diabetes accounts for approximately 95 percent of all cases. It is acquired, and lifestyle factors such as poor diet, inactivity, and the presence of pre-diabetes greatly increase a person's risk. About 80 to 90 percent of people with type 2 diabetes are overweight or obese. In type 2 diabetes, cells become resistant to the effects of insulin. In response, the pancreas increases its insulin secretion, but over time, the beta cells become exhausted. In many cases, type 2 diabetes can be reversed by moderate weight loss, regular physical activity, and consumption of a healthy diet; however, if blood glucose levels cannot be controlled, the person with diabetes will eventually require insulin.

Two of the early manifestations of diabetes are excessive urination and excessive thirst. They demonstrate how the out-of-control levels of glucose in the blood affect kidney function. The kidneys are responsible for filtering glucose from the blood. Excessive blood glucose draws water into the urine, and as a result the person eliminates an abnormally large quantity of sweet urine. The use of body water to dilute the urine leaves the body dehydrated, and so the person is unusually and continually thirsty. The person may also experience persistent hunger because the body cells are unable to access the glucose in the bloodstream.

Over time, persistently high levels of glucose in the blood injure tissues throughout the body, especially those of the blood vessels and nerves. Inflammation and injury of the lining of arteries lead to atherosclerosis and an increased risk of heart attack and stroke. Damage to the microscopic blood vessels of the kidney impairs kidney function and can lead to kidney failure. Damage to blood vessels that serve the eyes can lead to blindness.

Blood vessel damage also reduces circulation to the limbs, whereas nerve damage leads to a loss of sensation, called neuropathy, particularly in the hands and feet. Together, these changes increase the risk of injury, infection, and tissue death (necrosis), contributing to a high rate of toe, foot, and lower leg amputations in people with diabetes. Uncontrolled diabetes can also lead to a dangerous form of metabolic acidosis called ketoacidosis. Deprived of glucose, cells increasingly rely on fat stores for fuel. However, in a glucose-deficient state, the liver is forced to use an alternative lipid metabolism pathway that results in the increased production of ketone bodies (or ketones), which are acidic. The build-up of ketones in the blood causes ketoacidosis, which—if left untreated—may lead to a life-threatening “diabetic coma.” Together, these complications make diabetes the seventh leading cause of death in the United States.

Diabetes is diagnosed when lab tests reveal that blood glucose levels are higher than normal, a condition called **hyperglycemia**. The treatment of diabetes depends on the type, the severity of the condition, and the ability of the patient to make lifestyle changes. As noted earlier, moderate weight loss, regular physical activity, and consumption of a healthful diet can reduce blood glucose levels. Some patients with type 2 diabetes may be unable to control their disease with these lifestyle changes, and will require medication. Historically, the first-line treatment of type 2 diabetes was insulin. Research advances have resulted in alternative options, including medications that enhance pancreatic function.

### **INTERACTIVE LINK**

Visit this [link](http://openstax.org/l/insulin) (<http://openstax.org/l/insulin>) to view an animation describing the role of insulin and the pancreas in diabetes.

## 17.10 Organs with Secondary Endocrine Functions

### LEARNING OBJECTIVES

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

- Identify the organs with a secondary endocrine function, the hormone they produce, and its effects

In your study of anatomy and physiology, you have already encountered a few of the many organs of the body that have secondary endocrine functions. Here, you will learn about the hormone-producing activities of the heart, gastrointestinal tract, kidneys, skeleton, adipose tissue, skin, and thymus.

### Heart

When the body experiences an increase in blood volume or pressure, the cells of the heart's atrial wall stretch. In response, specialized cells in the wall of the atria produce and secrete the peptide hormone **atrial natriuretic**

**peptide (ANP).** ANP signals the kidneys to reduce sodium reabsorption, thereby decreasing the amount of water reabsorbed from the urine filtrate and reducing blood volume. Other actions of ANP include the inhibition of renin secretion, thus inhibition of the renin-angiotensin-aldosterone system (RAAS) and vasodilation. Therefore, ANP aids in decreasing blood pressure, blood volume, and blood sodium levels.

### Gastrointestinal Tract

The endocrine cells of the GI tract are located in the mucosa of the stomach and small intestine. Some of these hormones are secreted in response to eating a meal and aid in digestion. An example of a hormone secreted by the stomach cells is gastrin, a peptide hormone secreted in response to stomach distention that stimulates the release of hydrochloric acid. Secretin is a peptide hormone secreted by the small intestine as acidic chyme (partially digested food and fluid) moves from the stomach. It stimulates the release of bicarbonate from the pancreas, which buffers the acidic chyme, and inhibits the further secretion of hydrochloric acid by the stomach. Cholecystokinin (CCK) is another peptide hormone released from the small intestine. It promotes the secretion of pancreatic enzymes and the release of bile from the gallbladder, both of which facilitate digestion. Other hormones produced by the intestinal cells aid in glucose metabolism, such as by stimulating the pancreatic beta cells to secrete insulin, reducing glucagon secretion from the alpha cells, or enhancing cellular sensitivity to insulin.

### Kidneys

The kidneys participate in several complex endocrine pathways and produce certain hormones. A decline in blood flow to the kidneys stimulates them to release the enzyme renin, triggering the renin-angiotensin-aldosterone (RAAS) system, and stimulating the reabsorption of sodium and water. The reabsorption increases blood flow and blood pressure. The kidneys also play a role in regulating blood calcium levels through the production of calcitriol from vitamin D<sub>3</sub>, which is released in response to the secretion of parathyroid hormone (PTH). In addition, the kidneys produce the hormone **erythropoietin (EPO)** in response to low oxygen levels. EPO stimulates the production of red blood cells (erythrocytes) in the bone marrow, thereby increasing oxygen delivery to tissues. You may have heard of EPO as a performance-enhancing drug (in a synthetic form).

### Skeleton

Although bone has long been recognized as a target for hormones, only recently have researchers recognized that the skeleton itself produces at least two hormones. Fibroblast growth factor 23 (FGF23) is produced by bone cells in response to increased blood levels of vitamin D<sub>3</sub> or phosphate. It triggers the kidneys to inhibit the formation of calcitriol from vitamin D<sub>3</sub> and to increase phosphorus excretion. Osteocalcin, produced by osteoblasts, stimulates the pancreatic beta cells to increase insulin production. It also acts on peripheral tissues to increase their sensitivity to insulin and their utilization of glucose.

### Adipose Tissue

Adipose tissue produces and secretes several hormones involved in lipid metabolism and storage. One important example is **leptin**, a protein manufactured by adipose cells that circulates in amounts directly proportional to levels of body fat. Leptin is released in response to food consumption and acts by binding to brain neurons involved in energy intake and expenditure. Binding of leptin produces a feeling of satiety after a meal, thereby reducing appetite. It also appears that the binding of leptin to brain receptors triggers the sympathetic nervous system to regulate bone metabolism, increasing deposition of cortical bone. Adiponectin—another hormone synthesized by adipose cells—appears to reduce cellular insulin resistance and to protect blood vessels from inflammation and atherosclerosis. Its levels are lower in people who are obese, and rise following weight loss.

### Skin

The skin functions as an endocrine organ in the production of the inactive form of vitamin D<sub>3</sub>, cholecalciferol. When cholesterol present in the epidermis is exposed to ultraviolet radiation, it is converted to cholecalciferol, which then enters the blood. In the liver, cholecalciferol is converted to an intermediate that travels to the kidneys and is further converted to calcitriol, the active form of vitamin D<sub>3</sub>. Vitamin D is important in a variety of physiological processes, including intestinal calcium absorption and immune system function. In some studies, low levels of vitamin D have been associated with increased risks of cancer, severe asthma, and multiple sclerosis. Vitamin D deficiency in children causes rickets, and in adults, osteomalacia—both of which are characterized by bone deterioration.

## Thymus

The **thymus** is an organ of the immune system that is larger and more active during infancy and early childhood, and begins to atrophy as we age. Its endocrine function is the production of a group of hormones called **thymosins** that contribute to the development and differentiation of T lymphocytes, which are immune cells. Although the role of thymosins is not yet well understood, it is clear that they contribute to the immune response. Thymosins have been found in tissues other than the thymus and have a wide variety of functions, so the thymosins cannot be strictly categorized as thymic hormones.

## Liver

The liver is responsible for secreting at least four important hormones or hormone precursors: insulin-like growth factor (somatomedin), angiotensinogen, thrombopoietin, and hepcidin. Insulin-like growth factor-1 is the immediate stimulus for growth in the body, especially of the bones. Angiotensinogen is the precursor to angiotensin, mentioned earlier, which increases blood pressure. Thrombopoietin stimulates the production of the blood's platelets. Hepcids block the release of iron from cells in the body, helping to regulate iron homeostasis in our body fluids. The major hormones of these other organs are summarized in [Table 17.8](#).

Organs with Secondary Endocrine Functions and Their Major Hormones

Organ	Major hormones	Effects
Heart	Atrial natriuretic peptide (ANP)	Reduces blood volume, blood pressure, and $\text{Na}^+$ concentration
Gastrointestinal tract	Gastrin, secretin, and cholecystokinin	Aid digestion of food and buffering of stomach acids
Gastrointestinal tract	Glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1)	Stimulate beta cells of the pancreas to release insulin
Kidneys	Renin	Stimulates release of aldosterone
Kidneys	Calcitriol	Aids in the absorption of $\text{Ca}^{2+}$
Kidneys	Erythropoietin	Triggers the formation of red blood cells in the bone marrow
Skeleton	FGF23	Inhibits production of calcitriol and increases phosphate excretion
Skeleton	Osteocalcin	Increases insulin production
Adipose tissue	Leptin	Promotes satiety signals in the brain
Adipose tissue	Adiponectin	Reduces insulin resistance
Skin	Cholecalciferol	Modified to form vitamin D
Thymus (and other organs)	Thymosins	Among other things, aids in the development of T lymphocytes of the immune system

TABLE 17.8

Organ	Major hormones	Effects
Liver	Insulin-like growth factor-1	Stimulates bodily growth
Liver	Angiotensinogen	Raises blood pressure
Liver	Thrombopoietin	Causes increase in platelets
Liver	Hepcidin	Blocks release of iron into body fluids

**TABLE 17.8**

## 17.11 Development and Aging of the Endocrine System

### LEARNING OBJECTIVES

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

- Describe the embryonic origins of the endocrine system
- Discuss the effects of aging on the endocrine system

The endocrine system arises from all three embryonic germ layers. The endocrine glands that produce the steroid hormones, such as the gonads and adrenal cortex, arise from the mesoderm. In contrast, endocrine glands that arise from the endoderm and ectoderm produce the amine, peptide, and protein hormones. The pituitary gland arises from two distinct areas of the ectoderm: the anterior pituitary gland arises from the oral ectoderm, whereas the posterior pituitary gland arises from the neural ectoderm at the base of the hypothalamus. The pineal gland also arises from the ectoderm. The two structures of the adrenal glands arise from two different germ layers: the adrenal cortex from the mesoderm and the adrenal medulla from ectoderm neural cells. The endoderm gives rise to the thyroid and parathyroid glands, as well as the pancreas and the thymus.

As the body ages, changes occur that affect the endocrine system, sometimes altering the production, secretion, and catabolism of hormones. For example, the structure of the anterior pituitary gland changes as vascularization decreases and the connective tissue content increases with increasing age. This restructuring affects the gland's hormone production. For example, the amount of human growth hormone that is produced declines with age, resulting in the reduced muscle mass commonly observed in the elderly.

The adrenal glands also undergo changes as the body ages; as fibrous tissue increases, the production of cortisol and aldosterone decreases. Interestingly, the production and secretion of epinephrine and norepinephrine remain normal throughout the aging process.

A well-known example of the aging process affecting an endocrine gland is menopause and the decline of ovarian function. With increasing age, the ovaries decrease in both size and weight and become progressively less sensitive to gonadotropins. This gradually causes a decrease in estrogen and progesterone levels, leading to menopause and the inability to reproduce. Low levels of estrogens and progesterone are also associated with some disease states, such as osteoporosis, atherosclerosis, and hyperlipidemia, or abnormal blood lipid levels.

Testosterone levels also decline with age, a condition called andropause (or viropause); however, this decline is much less dramatic than the decline of estrogens, and much more gradual, rarely affecting sperm production until very old age. Although this means that males maintain their ability to produce offspring for decades longer than females, the quantity, quality, and motility of their sperm is often reduced.

As the body ages, the thyroid gland produces less of the thyroid hormones, causing a gradual decrease in the basal metabolic rate. The lower metabolic rate reduces the production of body heat and increases levels of body fat. Parathyroid hormones, on the other hand, increase with age. This may be because of reduced dietary calcium levels, causing a compensatory increase in parathyroid hormone. However, increased parathyroid hormone levels combined with decreased levels of calcitonin (and estrogens in females) can lead to osteoporosis as PTH stimulates demineralization of bones to increase blood calcium levels. Notice that osteoporosis is common in all elderly people regardless of sex.

Increasing age also affects glucose metabolism, as blood glucose levels spike more rapidly and take longer to return to normal in the elderly. In addition, increasing glucose intolerance may occur because of a gradual decline in cellular insulin sensitivity. Almost 27 percent of Americans aged 65 and older have diabetes.

## Key Terms

- acromegaly** disorder in adults caused when abnormally high levels of GH trigger growth of bones in the face, hands, and feet
- adenylyl cyclase** membrane-bound enzyme that converts ATP to cyclic AMP, creating cAMP, as a result of G-protein activation
- adrenal cortex** outer region of the adrenal glands consisting of multiple layers of epithelial cells and capillary networks that produces mineralocorticoids and glucocorticoids
- adrenal glands** endocrine glands located at the top of each kidney that are important for the regulation of the stress response, blood pressure and blood volume, water homeostasis, and electrolyte levels
- adrenal medulla** inner layer of the adrenal glands that plays an important role in the stress response by producing epinephrine and norepinephrine
- adrenocorticotrophic hormone (ACTH)** anterior pituitary hormone that stimulates the adrenal cortex to secrete corticosteroid hormones (also called corticotropin)
- alarm reaction** the short-term stress, or the fight-or-flight response, of stage one of the general adaptation syndrome mediated by the hormones epinephrine and norepinephrine
- aldosterone** hormone produced and secreted by the adrenal cortex that stimulates sodium and fluid retention and increases blood volume and blood pressure
- alpha cell** pancreatic islet cell type that produces the hormone glucagon
- angiotensin-converting enzyme** the enzyme that converts angiotensin I to angiotensin II
- antidiuretic hormone (ADH)** hypothalamic hormone that is stored by the posterior pituitary and that signals the kidneys to reabsorb water
- atrial natriuretic peptide (ANP)** peptide hormone produced by the walls of the atria in response to high blood pressure, blood volume, or blood sodium that reduces the reabsorption of sodium and water in the kidneys and promotes vasodilation
- autocrine** chemical signal that elicits a response in the same cell that secreted it
- beta cell** pancreatic islet cell type that produces the hormone insulin
- calcitonin** peptide hormone produced and secreted by the parafollicular cells (C cells) of the thyroid gland that functions to decrease blood calcium levels
- chromaffin** neuroendocrine cells of the adrenal medulla
- colloid** viscous fluid in the central cavity of thyroid follicles, containing the glycoprotein thyroglobulin
- cortisol** glucocorticoid important in gluconeogenesis, the catabolism of glycogen, and downregulation of the immune system
- cyclic adenosine monophosphate (cAMP)** second messenger that, in response to adenylyl cyclase activation, triggers a phosphorylation cascade
- delta cell** minor cell type in the pancreas that secretes the hormone somatostatin
- diabetes mellitus** condition caused by destruction or dysfunction of the beta cells of the pancreas or cellular resistance to insulin that results in abnormally high blood glucose levels
- diacylglycerol (DAG)** molecule that, like cAMP, activates protein kinases, thereby initiating a phosphorylation cascade
- downregulation** decrease in the number of hormone receptors, typically in response to chronically excessive levels of a hormone
- endocrine gland** tissue or organ that secretes hormones into the blood and lymph without ducts such that they may be transported to organs distant from the site of secretion
- endocrine system** cells, tissues, and organs that secrete hormones as a primary or secondary function and play an integral role in normal bodily processes
- epinephrine** primary and most potent catecholamine hormone secreted by the adrenal medulla in response to short-term stress; also called adrenaline
- erythropoietin (EPO)** protein hormone secreted in response to low oxygen levels that triggers the bone marrow to produce red blood cells
- estrogens** class of predominantly female sex hormones important for the development and growth of the female reproductive tract, secondary sex characteristics, the female reproductive cycle, and the maintenance of pregnancy
- exocrine system** cells, tissues, and organs that secrete substances directly to target tissues via glandular ducts
- first messenger** hormone that binds to a cell membrane hormone receptor and triggers activation of a second messenger system
- follicle-stimulating hormone (FSH)** anterior pituitary hormone that stimulates the production and maturation of sex cells
- G protein** protein associated with a cell membrane hormone receptor that initiates the next step in a second messenger system upon activation by hormone–receptor binding

- general adaptation syndrome (GAS)** the human body's three-stage response pattern to short- and long-term stress
- gigantism** disorder in children caused when abnormally high levels of GH prompt excessive growth
- glucagon** pancreatic hormone that stimulates the catabolism of glycogen to glucose, thereby increasing blood glucose levels
- glucocorticoids** hormones produced by the zona fasciculata of the adrenal cortex that influence glucose metabolism
- goiter** enlargement of the thyroid gland either as a result of iodine deficiency or hyperthyroidism
- gonadotropins** hormones that regulate the function of the gonads
- growth hormone (GH)** anterior pituitary hormone that promotes tissue building and influences nutrient metabolism (also called somatotropin)
- hormone** secretion of an endocrine organ that travels via the bloodstream or lymphatics to induce a response in target cells or tissues in another part of the body
- hormone receptor** protein within a cell or on the cell membrane that binds a hormone, initiating the target cell response
- hyperglycemia** abnormally high blood glucose levels
- hyperparathyroidism** disorder caused by overproduction of PTH that results in abnormally elevated blood calcium
- hyperthyroidism** clinically abnormal, elevated level of thyroid hormone in the blood; characterized by an increased metabolic rate, excess body heat, sweating, diarrhea, weight loss, and increased heart rate
- hypoparathyroidism** disorder caused by underproduction of PTH that results in abnormally low blood calcium
- hypophyseal portal system** network of blood vessels that enables hypothalamic hormones to travel into the anterior lobe of the pituitary without entering the systemic circulation
- hypothalamus** region of the diencephalon inferior to the thalamus that functions in neural and endocrine signaling
- hypothyroidism** clinically abnormal, low level of thyroid hormone in the blood; characterized by low metabolic rate, weight gain, cold extremities, constipation, and reduced mental activity
- infundibulum** stalk containing vasculature and neural tissue that connects the pituitary gland to the hypothalamus (also called the pituitary stalk)
- inhibin** hormone secreted by the male and female gonads that inhibits FSH production by the anterior pituitary
- inositol triphosphate (IP<sub>3</sub>)** molecule that initiates the release of calcium ions from intracellular stores
- insulin** pancreatic hormone that enhances the cellular uptake and utilization of glucose, thereby decreasing blood glucose levels
- insulin-like growth factors (IGF)** protein that enhances cellular proliferation, inhibits apoptosis, and stimulates the cellular uptake of amino acids for protein synthesis
- leptin** protein hormone secreted by adipose tissues in response to food consumption that promotes satiety
- luteinizing hormone (LH)** anterior pituitary hormone that triggers ovulation and the production of ovarian hormones, and the production of testosterone
- melatonin** amino acid-derived hormone that is secreted in response to low light and causes drowsiness
- mineralocorticoids** hormones produced by the zona glomerulosa cells of the adrenal cortex that influence fluid and electrolyte balance
- neonatal hypothyroidism** condition characterized by cognitive deficits, short stature, and other signs and symptoms in people born to people who were iodine-deficient during pregnancy
- norepinephrine** secondary catecholamine hormone secreted by the adrenal medulla in response to short-term stress; also called noradrenaline
- osmoreceptor** hypothalamic sensory receptor that is stimulated by changes in solute concentration (osmotic pressure) in the blood
- oxytocin** hypothalamic hormone stored in the posterior pituitary gland and important in stimulating uterine contractions in labor, milk ejection during breastfeeding, and feelings of attachment (produced by males and females)
- pancreas** organ with both exocrine and endocrine functions located posterior to the stomach that is important for digestion and the regulation of blood glucose
- pancreatic islets** specialized clusters of pancreatic cells that have endocrine functions; also called islets of Langerhans
- paracrine** chemical signal that elicits a response in neighboring cells; also called paracrine factor
- parathyroid glands** small, round glands embedded in the posterior thyroid gland that produce parathyroid hormone (PTH)
- parathyroid hormone (PTH)** peptide hormone produced and secreted by the parathyroid glands in response to low blood calcium levels

**phosphodiesterase (PDE)** cytosolic enzyme that deactivates and degrades cAMP

**phosphorylation cascade** signaling event in which multiple protein kinases phosphorylate the next protein substrate by transferring a phosphate group from ATP to the protein

**pineal gland** endocrine gland that secretes melatonin, which is important in regulating the sleep-wake cycle

**pinealocyte** cell of the pineal gland that produces and secretes the hormone melatonin

**pituitary dwarfism** disorder in children caused when abnormally low levels of GH result in growth retardation

**pituitary gland** bean-sized organ suspended from the hypothalamus that produces, stores, and secretes hormones in response to hypothalamic stimulation (also called hypophysis)

**PP cell** minor cell type in the pancreas that secretes the hormone pancreatic polypeptide

**progesterone** predominantly female sex hormone important in regulating the female reproductive cycle and the maintenance of pregnancy

**prolactin (PRL)** anterior pituitary hormone that promotes development of the mammary glands and the production of breast milk

**protein kinase** enzyme that initiates a phosphorylation cascade upon activation

**second messenger** molecule that initiates a signaling cascade in response to hormone binding on a cell membrane receptor and activation of a G protein

**stage of exhaustion** stage three of the general adaptation syndrome; the body's long-term response to stress mediated by the hormones of the adrenal cortex

**stage of resistance** stage two of the general adaptation syndrome; the body's continued

## Chapter Review

### 17.1 An Overview of the Endocrine System

The endocrine system consists of cells, tissues, and organs that secrete hormones critical to homeostasis. The body coordinates its functions through two major types of communication: neural and endocrine. Neural communication includes both electrical and chemical signaling between neurons and target cells. Endocrine communication involves chemical signaling via the release of hormones into the extracellular fluid. From there, hormones diffuse into the bloodstream and may travel to distant body regions, where they elicit a response in target cells. Endocrine glands are ductless glands that secrete hormones. Many organs of the body with other primary functions—such as the heart,

response to stress after stage one diminishes

**testosterone** steroid hormone secreted by the testes and important in the maturation of sperm cells, growth and development of the reproductive system, and the development of secondary sex characteristics

**thymosins** hormones produced and secreted by the thymus that play an important role in the development and differentiation of T cells

**thymus** organ that is involved in the development and maturation of T-cells and is particularly active during infancy and childhood

**thyroid gland** large endocrine gland responsible for the synthesis of thyroid hormones

**thyroid-stimulating hormone (TSH)** anterior pituitary hormone that triggers secretion of thyroid hormones by the thyroid gland (also called thyrotropin)

**thyroxine** (also, tetraiodothyronine, T<sub>4</sub>) amino acid-derived thyroid hormone that is more abundant but less potent than T<sub>3</sub> and often converted to T<sub>3</sub> by target cells

**triiodothyronine** (also, T<sub>3</sub>) amino acid-derived thyroid hormone that is less abundant but more potent than T<sub>4</sub>

**upregulation** increase in the number of hormone receptors, typically in response to chronically reduced levels of a hormone

**zona fasciculata** intermediate region of the adrenal cortex that produce hormones called glucocorticoids

**zona glomerulosa** most superficial region of the adrenal cortex, which produces the hormones collectively referred to as mineralocorticoids

**zona reticularis** deepest region of the adrenal cortex, which produces the steroid sex hormones called androgens

stomach, and kidneys—also have hormone-secreting cells.

### 17.2 Hormones

Hormones are derived from amino acids or lipids. Amine hormones originate from the amino acids tryptophan or tyrosine. Larger amino acid hormones include peptides and protein hormones. Steroid hormones are derived from cholesterol.

Steroid hormones and thyroid hormone are lipid soluble. All other amino acid-derived hormones are water soluble. Hydrophobic hormones are able to diffuse through the membrane and interact with an intracellular receptor. In contrast, hydrophilic

hormones must interact with cell membrane receptors. These are typically associated with a G protein, which becomes activated when the hormone binds the receptor. This initiates a signaling cascade that involves a second messenger, such as cyclic adenosine monophosphate (cAMP). Second messenger systems greatly amplify the hormone signal, creating a broader, more efficient, and faster response.

Hormones are released upon stimulation that is of either chemical or neural origin. Regulation of hormone release is primarily achieved through negative feedback. Various stimuli may cause the release of hormones, but there are three major types. Humoral stimuli are changes in ion or nutrient levels in the blood. Hormonal stimuli are changes in hormone levels that initiate or inhibit the secretion of another hormone. Finally, a neural stimulus occurs when a nerve impulse prompts the secretion or inhibition of a hormone.

### 17.3 The Pituitary Gland and Hypothalamus

The hypothalamus–pituitary complex is located in the diencephalon of the brain. The hypothalamus and the pituitary gland are connected by a structure called the infundibulum, which contains vasculature and nerve axons. The pituitary gland is divided into two distinct structures with different embryonic origins. The posterior lobe houses the axon terminals of hypothalamic neurons. It stores and releases into the bloodstream two hypothalamic hormones: oxytocin and antidiuretic hormone (ADH). The anterior lobe is connected to the hypothalamus by vasculature in the infundibulum and produces and secretes six hormones. Their secretion is regulated, however, by releasing and inhibiting hormones from the hypothalamus. The six anterior pituitary hormones are: growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL).

### 17.4 The Thyroid Gland

The thyroid gland is a butterfly-shaped organ located in the neck anterior to the trachea. Its hormones regulate basal metabolism, oxygen use, nutrient metabolism, the production of ATP, and calcium homeostasis. They also contribute to protein synthesis and the normal growth and development of body tissues, including maturation of the nervous system, and they increase the body's sensitivity to catecholamines. The thyroid hormones triiodothyronine ( $T_3$ ) and thyroxine ( $T_4$ ) are produced and secreted by the thyroid gland in response to thyroid-stimulating hormone (TSH) from

the anterior pituitary. Synthesis of the amino acid-derived  $T_3$  and  $T_4$  hormones requires iodine. Insufficient amounts of iodine in the diet can lead to goiter, cretinism, and many other disorders.

### 17.5 The Parathyroid Glands

Calcium is required for a variety of important physiologic processes, including neuromuscular functioning; thus, blood calcium levels are closely regulated. The parathyroid glands are small structures located on the posterior thyroid gland that produce parathyroid hormone (PTH), which regulates blood calcium levels. Low blood calcium levels cause the production and secretion of PTH. In contrast, elevated blood calcium levels inhibit secretion of PTH and trigger secretion of the thyroid hormone calcitonin. Underproduction of PTH can result in hypoparathyroidism. In contrast, overproduction of PTH can result in hyperparathyroidism.

### 17.6 The Adrenal Glands

The adrenal glands, located superior to each kidney, consist of two regions: the adrenal cortex and adrenal medulla. The adrenal cortex—the outer layer of the gland—produces mineralocorticoids, glucocorticoids, and androgens. The adrenal medulla at the core of the gland produces epinephrine and norepinephrine.

The adrenal glands mediate a short-term stress response and a long-term stress response. A perceived threat results in the secretion of epinephrine and norepinephrine from the adrenal medulla, which mediate the fight-or-flight response. The long-term stress response is mediated by the secretion of CRH from the hypothalamus, which triggers ACTH, which in turn stimulates the secretion of corticosteroids from the adrenal cortex. The mineralocorticoids, chiefly aldosterone, cause sodium and fluid retention, which increases blood volume and blood pressure.

### 17.7 The Pineal Gland

The pineal gland is an endocrine structure of the diencephalon of the brain, and is located inferior and posterior to the thalamus. It is made up of pinealocytes. These cells produce and secrete the hormone melatonin in response to low light levels. High blood levels of melatonin induce drowsiness. Jet lag, caused by traveling across several time zones, occurs because melatonin synthesis takes several days to readjust to the light-dark patterns in the new environment.

## 17.8 Gonadal and Placental Hormones

The reproductive system is regulated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH) produced by the anterior lobe of the pituitary gland in response to gonadotropin-releasing hormone (GnRH) from the hypothalamus. FSH stimulates sperm maturation, which is inhibited by the hormone inhibin. The steroid hormone testosterone, a type of androgen, is released in response to LH and is responsible for the maturation and maintenance of the testicular reproductive system, as well as the development of secondary sex characteristics. FSH also promotes egg maturation and LH signals the secretion of the sex hormones, the estrogens and progesterone. Both of these hormones are important in the development and maintenance of the ovarian reproductive system, as well as maintaining pregnancy. The placenta develops during early pregnancy, and secretes several hormones important for maintaining the pregnancy.

## 17.9 The Endocrine Pancreas

The pancreas has both exocrine and endocrine functions. The pancreatic islet cell types include alpha cells, which produce glucagon; beta cells, which produce insulin; delta cells, which produce somatostatin; and PP cells, which produce pancreatic polypeptide. Insulin and glucagon are involved in the regulation of glucose metabolism. Insulin is produced by the beta cells in response to high blood glucose levels. It enhances glucose uptake and utilization by target cells, as well as the storage of excess glucose for later use. Dysfunction of the production of insulin or

target cell resistance to the effects of insulin causes diabetes mellitus, a disorder characterized by high blood glucose levels. The hormone glucagon is produced and secreted by the alpha cells of the pancreas in response to low blood glucose levels. Glucagon stimulates mechanisms that increase blood glucose levels, such as the catabolism of glycogen into glucose.

## 17.10 Organs with Secondary Endocrine Functions

Some organs have a secondary endocrine function. For example, the walls of the atria of the heart produce the hormone atrial natriuretic peptide (ANP), the gastrointestinal tract produces the hormones gastrin, secretin, and cholecystokinin, which aid in digestion, and the kidneys produce erythropoietin (EPO), which stimulates the formation of red blood cells. Even bone, adipose tissue, and the skin have secondary endocrine functions.

## 17.11 Development and Aging of the Endocrine System

The endocrine system originates from all three germ layers of the embryo, including the endoderm, ectoderm, and mesoderm. In general, different hormone classes arise from distinct germ layers. Aging affects the endocrine glands, potentially affecting hormone production and secretion, and can cause disease. The production of hormones, such as human growth hormone, cortisol, aldosterone, sex hormones, and the thyroid hormones, decreases with age.

## Interactive Link Questions

1. Visit this [link](http://openstax.org/l/hormonebind) (<http://openstax.org/l/hormonebind>) to watch an animation of the events that occur when a hormone binds to a cell membrane receptor. What is the secondary messenger made by adenylyl cyclase during the activation of liver cells by epinephrine?
2. Visit this [link](http://openstax.org/l/roleofhypo) (<http://openstax.org/l/roleofhypo>) to watch an animation showing the role of the hypothalamus and the pituitary gland. Which hormone is released by the pituitary to stimulate the thyroid gland?
3. Visit this [link](http://openstax.org/l/adrenalglands) (<http://openstax.org/l/adrenalglands>) to view an animation describing the location and function of the adrenal glands. Which hormone produced by the adrenal glands is responsible for mobilization of energy stores?
4. Visit this [link](http://openstax.org/l/melatonin) (<http://openstax.org/l/melatonin>) to view an animation describing the function of the hormone melatonin. What should you avoid doing in the middle of your sleep cycle that would lower melatonin?
5. Visit this [link](http://openstax.org/l/pancreas1) (<http://openstax.org/l/pancreas1>) to view an animation describing the location and function of the pancreas. What goes wrong in the function of insulin in type 2 diabetes?

## Review Questions

- 6.** Endocrine glands \_\_\_\_\_.  
 a. secrete hormones that travel through a duct to the target organs  
 b. release neurotransmitters into the synaptic cleft  
 c. secrete chemical messengers that travel in the bloodstream  
 d. include sebaceous glands and sweat glands
- 7.** Chemical signaling that affects neighboring cells is called \_\_\_\_\_.  
 a. autocrine  
 b. paracrine  
 c. endocrine  
 d. neuron
- 8.** A newly developed pesticide has been observed to bind to an intracellular hormone receptor. If ingested, residue from this pesticide could disrupt levels of \_\_\_\_\_.  
 a. melatonin  
 b. thyroid hormone  
 c. growth hormone  
 d. insulin
- 9.** A small molecule binds to a G protein, preventing its activation. What direct effect will this have on signaling that involves cAMP?  
 a. The hormone will not be able to bind to the hormone receptor.  
 b. Adenylyl cyclase will not be activated.  
 c. Excessive quantities of cAMP will be produced.  
 d. The phosphorylation cascade will be initiated.
- 10.** A student is in a car accident, and although not hurt, immediately experiences pupil dilation, increased heart rate, and rapid breathing. What type of endocrine system stimulus did the student receive?  
 a. humoral  
 b. hormonal  
 c. neural  
 d. positive feedback
- 11.** The hypothalamus is functionally and anatomically connected to the posterior pituitary lobe by a bridge of \_\_\_\_\_.  
 a. blood vessels  
 b. nerve axons  
 c. cartilage  
 d. bone
- 12.** Which of the following is an anterior pituitary hormone?  
 a. ADH  
 b. oxytocin  
 c. TSH  
 d. cortisol
- 13.** How many hormones are produced by the posterior pituitary?  
 a. 0  
 b. 1  
 c. 2  
 d. 6
- 14.** Which of the following hormones contributes to the regulation of the body's fluid and electrolyte balance?  
 a. adrenocorticotropic hormone  
 b. antidiuretic hormone  
 c. luteinizing hormone  
 d. all of the above
- 15.** Which of the following statements about the thyroid gland is true?  
 a. It is located anterior to the trachea and inferior to the larynx.  
 b. The parathyroid glands are embedded within it.  
 c. It manufactures three hormones.  
 d. all of the above
- 16.** The secretion of thyroid hormones is controlled by \_\_\_\_\_.  
 a. TSH from the hypothalamus  
 b. TSH from the anterior pituitary  
 c. thyroxine from the anterior pituitary  
 d. thyroglobulin from the thyroid's parafollicular cells
- 17.** The development of a goiter indicates that \_\_\_\_\_.  
 a. the anterior pituitary is abnormally enlarged  
 b. there is hypertrophy of the thyroid's follicle cells  
 c. there is an excessive accumulation of colloid in the thyroid follicles  
 d. the anterior pituitary is secreting excessive growth hormone

- 18.** Iodide ions cross from the bloodstream into follicle cells via \_\_\_\_\_.
- simple diffusion
  - facilitated diffusion
  - active transport
  - osmosis
- 19.** When blood calcium levels are low, PTH stimulates \_\_\_\_\_.
- urinary excretion of calcium by the kidneys
  - a reduction in calcium absorption from the intestines
  - the activity of osteoblasts
  - the activity of osteoclasts
- 20.** Which of the following can result from hyperparathyroidism?
- increased bone deposition
  - fractures
  - convulsions
  - all of the above
- 21.** The adrenal glands are attached superiorly to which organ?
- thyroid
  - liver
  - kidneys
  - hypothalamus
- 22.** What secretory cell type is found in the adrenal medulla?
- chromaffin cells
  - neuroglial cells
  - follicle cells
  - oxyphil cells
- 23.** Cushing's disease is a disorder caused by \_\_\_\_\_.
- abnormally low levels of cortisol
  - abnormally high levels of cortisol
  - abnormally low levels of aldosterone
  - abnormally high levels of aldosterone
- 24.** Which of the following responses is not part of the fight-or-flight response?
- pupil dilation
  - increased oxygen supply to the lungs
  - suppressed digestion
  - reduced mental activity
- 25.** What cells secrete melatonin?
- melanocytes
  - pinealocytes
  - suprachiasmatic nucleus cells
  - retinal cells
- 26.** The production of melatonin is inhibited by \_\_\_\_\_.
- declining levels of light
  - exposure to bright light
  - the secretion of serotonin
  - the activity of pinealocytes
- 27.** The gonads produce what class of hormones?
- amine hormones
  - peptide hormones
  - steroid hormones
  - catecholamines
- 28.** The production of FSH by the anterior pituitary is reduced by which hormone?
- estrogens
  - progesterone
  - relaxin
  - inhibin
- 29.** The function of the placental hormone human placental lactogen (hPL) is to \_\_\_\_\_.
- prepare the breasts for lactation
  - nourish the placenta
  - regulate the menstrual cycle
  - all of the above
- 30.** If an autoimmune disorder targets the alpha cells, production of which hormone would be directly affected?
- somatostatin
  - pancreatic polypeptide
  - insulin
  - glucagon
- 31.** Which of the following statements about insulin is true?
- Insulin acts as a transport protein, carrying glucose across the cell membrane.
  - Insulin facilitates the movement of intracellular glucose transporters to the cell membrane.
  - Insulin stimulates the breakdown of stored glycogen into glucose.
  - Insulin stimulates the kidneys to reabsorb glucose into the bloodstream.
- 32.** The walls of the atria produce which hormone?
- cholecystokinin
  - atrial natriuretic peptide
  - renin
  - calcitriol

- 33.** The end result of the RAAS is to \_\_\_\_\_.  
 a. reduce blood volume  
 b. increase blood glucose  
 c. reduce blood pressure  
 d. increase blood pressure
- 34.** Athletes may take synthetic EPO to boost their \_\_\_\_\_.  
 a. blood calcium levels  
 b. secretion of growth hormone  
 c. blood oxygen levels  
 d. muscle mass
- 35.** Hormones produced by the thymus play a role in the \_\_\_\_\_.  
 a. development of T cells  
 b. preparation of the body for childbirth  
 c. regulation of appetite  
 d. release of hydrochloric acid in the stomach
- 36.** The anterior pituitary gland develops from which embryonic germ layer?  
 a. oral ectoderm  
 b. neural ectoderm  
 c. mesoderm  
 d. endoderm
- 37.** In the elderly, decreased thyroid function causes \_\_\_\_\_.  
 a. increased tolerance for cold  
 b. decreased basal metabolic rate  
 c. decreased body fat  
 d. osteoporosis

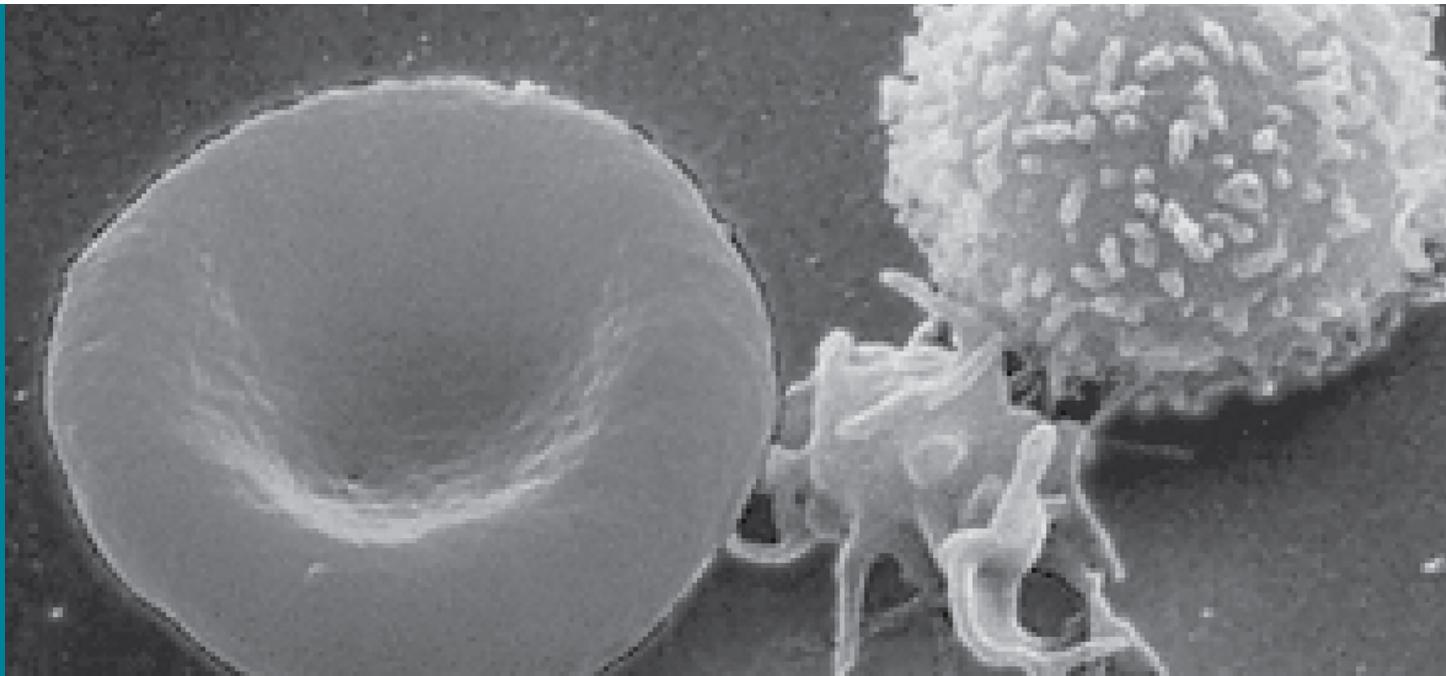
## Critical Thinking Questions

- 38.** Describe several main differences in the communication methods used by the endocrine system and the nervous system.
- 39.** Compare and contrast endocrine and exocrine glands.
- 40.** True or false: Neurotransmitters are a special class of paracrines. Explain your answer.
- 41.** Compare and contrast the signaling events involved with the second messengers cAMP and IP<sub>3</sub>.
- 42.** Describe the mechanism of hormone response resulting from the binding of a hormone with an intracellular receptor.
- 43.** Compare and contrast the anatomical relationship of the anterior and posterior lobes of the pituitary gland to the hypothalamus.
- 44.** Name the target tissues for prolactin.
- 45.** Explain why maternal iodine deficiency might lead to neurological impairment in the fetus.
- 46.** Define hyperthyroidism and explain why one of its symptoms is weight loss.
- 47.** Describe the role of negative feedback in the function of the parathyroid gland.
- 48.** Explain why someone with a parathyroid gland tumor might develop kidney stones.
- 49.** What are the three regions of the adrenal cortex and what hormones do they produce?
- 50.** If innervation to the adrenal medulla were disrupted, what would be the physiological outcome?
- 51.** Compare and contrast the short-term and long-term stress response.
- 52.** Seasonal affective disorder (SAD) is a mood disorder characterized by, among other symptoms, increased appetite, sluggishness, and increased sleepiness. It occurs most commonly during the winter months, especially in regions with long winter nights. Propose a role for melatonin in SAD and a possible non-drug therapy.
- 53.** Retinitis pigmentosa (RP) is a disease that causes deterioration of the retinas of the eyes. Describe the impact RP would have on melatonin levels.
- 54.** Compare and contrast the role of estrogens and progesterone.
- 55.** Describe the role of placental secretion of relaxin in preparation for childbirth.
- 56.** What would be the physiological consequence of a disease that destroyed the beta cells of the pancreas?
- 57.** Why is foot care extremely important for people with diabetes mellitus?
- 58.** Summarize the role of GI tract hormones following a meal.
- 59.** Compare and contrast the thymus gland in infancy and adulthood.
- 60.** Distinguish between the effects of menopause and andropause on fertility.



## CHAPTER 18

# The Cardiovascular System: Blood



**Figure 18.1** **Blood Cells** A single drop of blood contains millions of red blood cells, white blood cells, and platelets. One of each type is shown here, isolated from a scanning electron micrograph.

## CHAPTER 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

**INTRODUCTION** 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.

## 18.1 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.

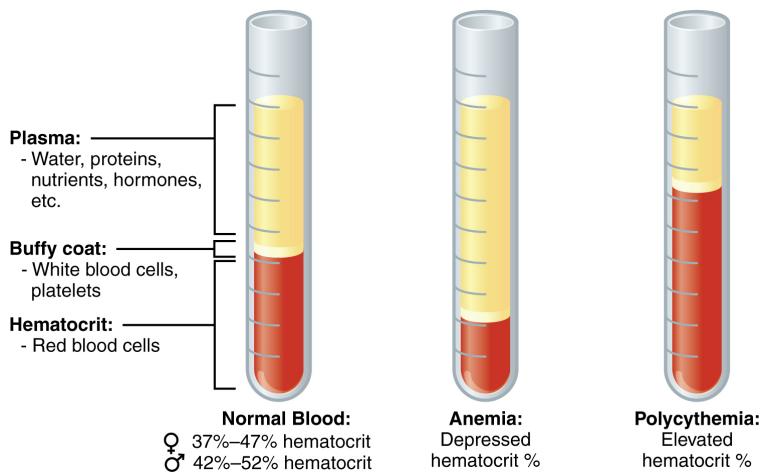
Blood also helps to maintain the chemical balance of the body. Proteins and other compounds in blood act as buffers, which thereby help to regulate the pH of body tissues. Blood also helps to regulate the water content of body cells.

## 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 18.2](#)). 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.

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).



**FIGURE 18.2 Composition of Blood** The cellular elements of blood include a vast number of erythrocytes and comparatively fewer leukocytes and platelets. Plasma is the fluid in which the formed elements are suspended. A sample of blood spun in a centrifuge reveals that plasma is the lightest component. It floats at the top of the tube separated from the heaviest elements, the erythrocytes, by a buffy coat of leukocytes and platelets. Hematocrit is the percentage of the total sample that is comprised of erythrocytes. Depressed and elevated hematocrit levels are shown for comparison.

### 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.

## INTERACTIVE LINK

Visit this [site](http://openstax.org/l/normallevels) (<http://openstax.org/l/normallevels>) 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 [Figure 18.3](#).

The three major groups of plasma proteins are as follows:

- **Albumin** is the most abundant of the plasma proteins. Manufactured by the liver, albumin molecules serve as binding proteins—transport vehicles for fatty acids and steroid hormones. Recall that lipids are hydrophobic; however, their binding to albumin enables their transport in the watery plasma. Albumin is also the most significant contributor to the osmotic pressure of blood; that is, its presence holds water inside the blood vessels and draws water from the tissues, across blood vessel walls, and into the bloodstream. This in turn helps to maintain both blood volume and blood pressure. Albumin normally accounts for approximately 54 percent of the total plasma protein content, in clinical levels of 3.5–5.0 g/dL blood.
- The second most common plasma proteins are the **globulins**. A heterogeneous group, there are three main subgroups known as alpha, beta, and gamma globulins. The alpha and beta globulins transport iron, lipids, and the fat-soluble vitamins A, D, E, and K to the cells; like albumin, they also contribute to osmotic pressure. The gamma globulins are proteins involved in immunity and are better known as an **antibodies** or **immunoglobulins**. Although other plasma proteins are produced by the liver, immunoglobulins are produced by specialized leukocytes known as plasma cells. (Seek additional content for more information about immunoglobulins.) Globulins make up approximately 38 percent of the total plasma protein volume, in clinical levels of 1.0–1.5 g/dL blood.
- **Fibrinogen** is the third of the three major groups of plasma proteins. Like albumin and the alpha and beta globulins, fibrinogen is produced by the liver. It is essential for blood clotting, 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.

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

FIGURE 18.3 Major Blood Components



## 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.

## 18.2 Production of the Formed Elements

### LEARNING OBJECTIVES

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

- Trace the generation of the formed elements of blood from bone marrow stem cells
- Discuss the role of hemopoietic growth factors in promoting the production of the formed elements

The lifespan of the formed elements is very brief. Although one type of leukocyte called memory cells can survive for years, most erythrocytes, leukocytes, and platelets normally live only a few hours to a few weeks. Thus, the body must form new blood cells and platelets quickly and continuously. When you donate a unit of blood during a blood drive (approximately 475 mL, or about 1 pint), your body typically replaces the donated plasma within 24 hours, but it takes about 4 to 6 weeks to replace the blood cells. This restricts the frequency with which donors can contribute their blood. The process by which this replacement occurs is called **hemopoiesis**, or hematopoiesis (from the Greek root *haima-* = "blood"; *-poiesis* = "production").

### Sites of Hemopoiesis

Prior to birth, hemopoiesis occurs in a number of tissues, beginning with the yolk sac of the developing embryo, and continuing in the fetal liver, spleen, lymphatic tissue, and eventually the red bone marrow. Following birth, most hemopoiesis occurs in the red marrow, a connective tissue within the spaces of spongy (cancellous) bone tissue. In children, hemopoiesis can occur in the medullary cavity of long bones; in adults, the process is largely restricted to the cranial and pelvic bones, the vertebrae, the sternum, and the proximal epiphyses of the femur and humerus.

Throughout adulthood, the liver and spleen maintain their ability to generate the formed elements. This process is referred to as extramedullary hemopoiesis (meaning hemopoiesis outside the medullary cavity of adult bones). When a disease such as bone cancer destroys the bone marrow, causing hemopoiesis to fail, extramedullary hemopoiesis may be initiated.

### Differentiation of Formed Elements from Stem Cells

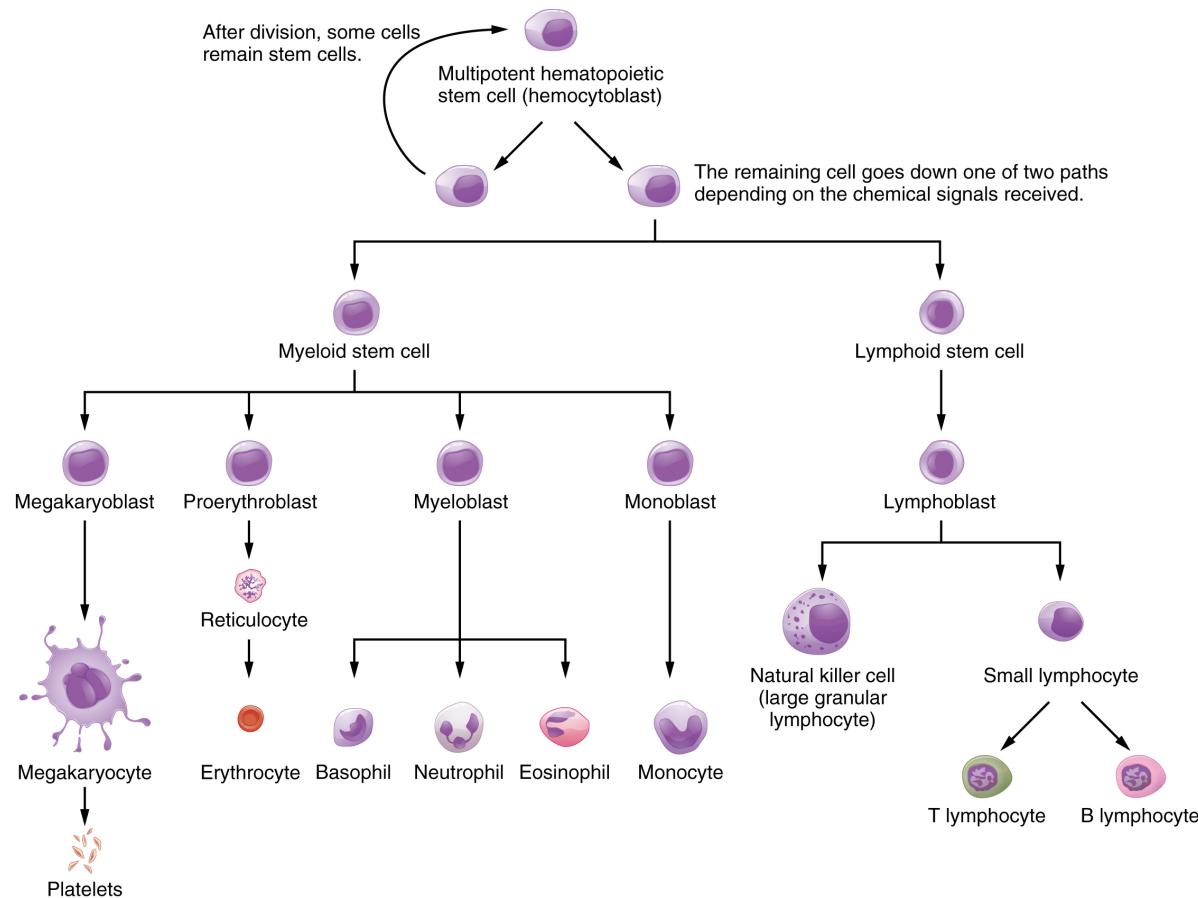
All formed elements arise from stem cells of the red bone marrow. Recall that stem cells undergo mitosis plus cytokinesis (cellular division) to give rise to new daughter cells: One of these remains a stem cell and the other differentiates into one of any number of diverse cell types. Stem cells may be viewed as occupying a hierarchical system, with some loss of the ability to diversify at each step. The **totipotent stem cell** is the zygote, or fertilized egg. The totipotent (*toti-* = "all") stem cell gives rise to all cells of the human body. The next level is the **pluripotent stem cell**, which gives rise to multiple types of cells of the body and some of the supporting fetal membranes.

Beneath this level, the mesenchymal cell is a stem cell that develops only into types of connective tissue, including fibrous connective tissue, bone, cartilage, and blood, but not epithelium, muscle, and nervous tissue. One step lower on the hierarchy of stem cells is the **hematopoietic stem cell**, or **hemocytoblast**. All of the formed elements of blood originate from this specific type of cell.

Hemopoiesis begins when the hematopoietic stem cell is exposed to appropriate chemical stimuli collectively called **hemopoietic growth factors**, which prompt it to divide and differentiate. One daughter cell remains a hematopoietic stem cell, allowing hemopoiesis to continue. The other daughter cell becomes either of two types of more

specialized stem cells (Figure 18.4):

- **Lymphoid stem cells** give rise to a class of leukocytes known as lymphocytes, which include the various T cells, B cells, and natural killer (NK) cells, all of which function in immunity. However, hemopoiesis of lymphocytes progresses somewhat differently from the process for the other formed elements. In brief, lymphoid stem cells quickly migrate from the bone marrow to lymphatic tissues, including the lymph nodes, spleen, and thymus, where their production and differentiation continues. B cells are so named since they mature in the bone marrow, while T cells mature in the thymus.
- **Myeloid stem cells** give rise to all the other formed elements, including the erythrocytes; megakaryocytes that produce platelets; and a myeloblast lineage that gives rise to monocytes and three forms of granular leukocytes: neutrophils, eosinophils, and basophils.



**FIGURE 18.4 Hematopoietic System of Bone Marrow** Hemopoiesis is the proliferation and differentiation of the formed elements of blood.

Lymphoid and myeloid stem cells do not immediately divide and differentiate into mature formed elements. As you can see in Figure 18.4, there are several intermediate stages of precursor cells (literally, forerunner cells), many of which can be recognized by their names, which have the suffix *-blast*. For instance, megakaryoblasts are the precursors of megakaryocytes, and proerythroblasts become reticulocytes, which eject their nucleus and most other organelles before maturing into erythrocytes.

### Hemopoietic Growth Factors

Development from stem cells to precursor cells to mature cells is again initiated by hemopoietic growth factors. These include the following:

- **Erythropoietin (EPO)** is a glycoprotein hormone secreted by the interstitial fibroblast cells of the kidneys in response to low oxygen levels. It prompts the production of erythrocytes. Some athletes use synthetic EPO as a performance-enhancing drug (called blood doping) to increase RBC counts and subsequently increase oxygen

delivery to tissues throughout the body. EPO is a banned substance in most organized sports, but it is also used medically in the treatment of certain anemia, specifically those triggered by certain types of cancer, and other disorders in which increased erythrocyte counts and oxygen levels are desirable.

- **Thrombopoietin**, another glycoprotein hormone, is produced by the liver and kidneys. It triggers the development of megakaryocytes into platelets.
- **Cytokines** are glycoproteins secreted by a wide variety of cells, including red bone marrow, leukocytes, macrophages, fibroblasts, and endothelial cells. They act locally as autocrine or paracrine factors, stimulating the proliferation of progenitor cells and helping to stimulate both nonspecific and specific resistance to disease. There are two major subtypes of cytokines known as colony-stimulating factors and interleukins.
  - **Colony-stimulating factors (CSFs)** are glycoproteins that act locally, as autocrine or paracrine factors. Some trigger the differentiation of myeloblasts into granular leukocytes, namely, neutrophils, eosinophils, and basophils. These are referred to as granulocyte CSFs. A different CSF induces the production of monocytes, called monocyte CSFs. Both granulocytes and monocytes are stimulated by GM-CSF; granulocytes, monocytes, platelets, and erythrocytes are stimulated by multi-CSF. Synthetic forms of these hormones are often administered to patients with various forms of cancer who are receiving chemotherapy to revive their WBC counts.
  - **Interleukins** are another class of cytokine signaling molecules important in hemopoiesis. They were initially thought to be secreted uniquely by leukocytes and to communicate only with other leukocytes, and were named accordingly, but are now known to be produced by a variety of cells including bone marrow and endothelium. Researchers now suspect that interleukins may play other roles in body functioning, including differentiation and maturation of cells, producing immunity and inflammation. To date, more than a dozen interleukins have been identified, with others likely to follow. They are generally numbered IL-1, IL-2, IL-3, etc.

### Everyday Connection

#### Blood Doping

In its original intent, the term blood doping was used to describe the practice of injecting by transfusion supplemental RBCs into an individual, typically to enhance performance in a sport. Additional RBCs would deliver more oxygen to the tissues, providing extra aerobic capacity, clinically referred to as VO<sub>2</sub> max. The source of the cells was either from the recipient (autologous) or from a donor with compatible blood (homologous). This practice was aided by the well-developed techniques of harvesting, concentrating, and freezing of the RBCs that could be later thawed and injected, yet still retain their functionality. These practices are considered illegal in virtually all sports and run the risk of infection, significantly increasing the viscosity of the blood and the potential for transmission of blood-borne pathogens if the blood was collected from another individual.

With the development of synthetic EPO in the 1980s, it became possible to provide additional RBCs by artificially stimulating RBC production in the bone marrow. Originally developed to treat patients suffering from anemia, renal failure, or cancer treatment, large quantities of EPO can be generated by recombinant DNA technology. Synthetic EPO is injected under the skin and can increase hematocrit for many weeks. It may also induce polycythemia and raise hematocrit to 70 or greater. This increased viscosity raises the resistance of the blood and forces the heart to pump more powerfully; in extreme cases, it has resulted in death. Other drugs such as cobalt II chloride have been shown to increase natural EPO gene expression. Blood doping has become problematic in many sports, especially cycling. Lance Armstrong, winner of seven Tour de France and many other cycling titles, was stripped of his victories and admitted to blood doping in 2013.

#### INTERACTIVE LINK

Watch this [video](http://openstax.org/l/doping) (<http://openstax.org/l/doping>) to see doctors discuss the dangers of blood doping in sports. What are the some potential side effects of blood doping?

#### Bone Marrow Sampling and Transplants

Sometimes, a healthcare provider will order a **bone marrow biopsy**, a diagnostic test of a sample of red bone

marrow, or a **bone marrow transplant**, a treatment in which a donor's healthy bone marrow—and its stem cells—replaces the faulty bone marrow of a patient. These tests and procedures are often used to assist in the diagnosis and treatment of various severe forms of anemia, such as thalassemia major and sickle cell anemia, as well as some types of cancer, specifically leukemia.

In the past, when a bone marrow sample or transplant was necessary, the procedure would have required inserting a large-bore needle into the region near the iliac crest of the pelvic bones (*os coxae*). This location was preferred, since its location close to the body surface makes it more accessible, and it is relatively isolated from most vital organs. Unfortunately, the procedure is quite painful.

Now, direct sampling of bone marrow can often be avoided. In many cases, stem cells can be isolated in just a few hours from a sample of a patient's blood. The isolated stem cells are then grown in culture using the appropriate hemopoietic growth factors, and analyzed or sometimes frozen for later use.

For an individual requiring a transplant, a matching donor is essential to prevent the immune system from destroying the donor cells—a phenomenon known as tissue rejection. To treat patients with bone marrow transplants, it is first necessary to destroy the patient's own diseased marrow through radiation and/or chemotherapy. Donor bone marrow stem cells are then intravenously infused. From the bloodstream, they establish themselves in the recipient's bone marrow.

## 18.3 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 ( $\mu\text{L}$ ) of blood, and females have approximately 4.8 million per  $\mu\text{L}$ . 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 ( $\mu\text{m}$ ) ([Figure 18.5](#)). 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.

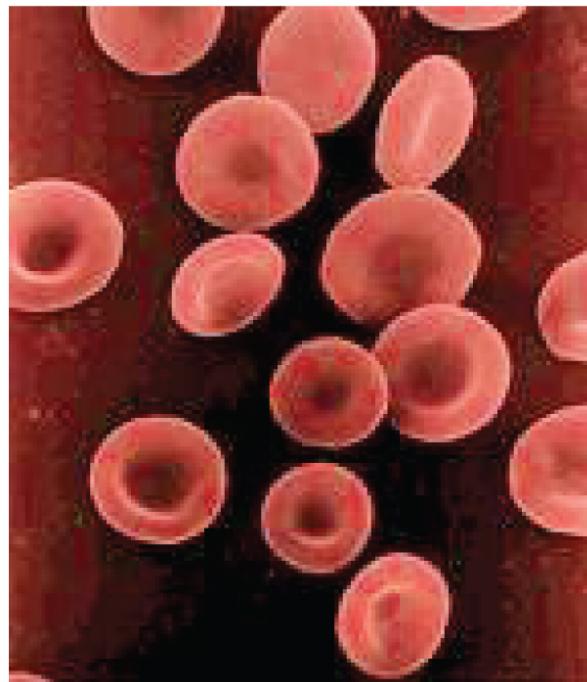
Formed element	Major subtypes	Numbers present per microliter ( $\mu\text{L}$ ) and mean (range)	Appearance in a standard blood smear	Summary of functions	Comments
Erythrocytes (red blood cells) 		5.2 million (4.4–6.0 million)	Flattened biconcave disk; no nucleus; pale red color	Transport oxygen and some carbon dioxide between tissues and lungs	Lifespan of approximately 120 days
Leukocytes (white blood cells)		7000 (5000–10,000)	Obvious dark-staining nucleus	All function in body defenses	Exit capillaries and move into tissues; lifespan of usually a few hours or days
Granulocytes including neutrophils, eosinophils, and basophils		4360 (1800–9950)	Abundant granules in cytoplasm; nucleus normally lobed	Nonspecific (innate) resistance to disease	Classified according to membrane-bound granules in cytoplasm
Neutrophils		4150 (1800–7300)	Nuclear lobes increase with age; pale lilac granules	Phagocytic; particularly effective against bacteria. Release cytotoxic chemicals from granules	Most common leukocyte; lifespan of minutes to days
Eosinophils		165 (0–700)	Nucleus generally two-lobed; bright red-orange granules	Phagocytic cells; particularly effective with antigen- antibody complexes. Release antihistamines. Increase in allergies and parasitic infections	Lifespan of minutes to days
Basophils		44 (0–150)	Nucleus generally two-lobed but difficult to see due to presence of heavy, dense, dark purple granules	Promotes inflammation	Least common leukocyte; lifespan unknown
Agranulocytes including lymphocytes and monocytes		2640 (1700–4950)	Lack abundant granules in cytoplasm; have a simple-shaped nucleus that may be indented	Body defenses	Group consists of two major cell types from different lineages
Lymphocytes	 	2185 (1500–4000)	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	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	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
Monocytes		455 (200–950)	Largest leukocyte with an indented or horseshoe-shaped nucleus	Very effective phagocytic cells engulfing pathogens or worn out cells; also serve as antigen-presenting cells (APCs) for other components of the immune system	Produced in red bone marrow; referred to as macrophages after leaving circulation
Platelets		350,000 (150,000–500,000)	Cellular fragments surrounded by a plasma membrane and containing granules; purple stain	Hemostasis plus release growth factors for repair and healing of tissue	Formed from megakaryocytes that remain in the red bone marrow and shed platelets into circulation

**FIGURE 18.5** 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 18.6](#)). 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.”

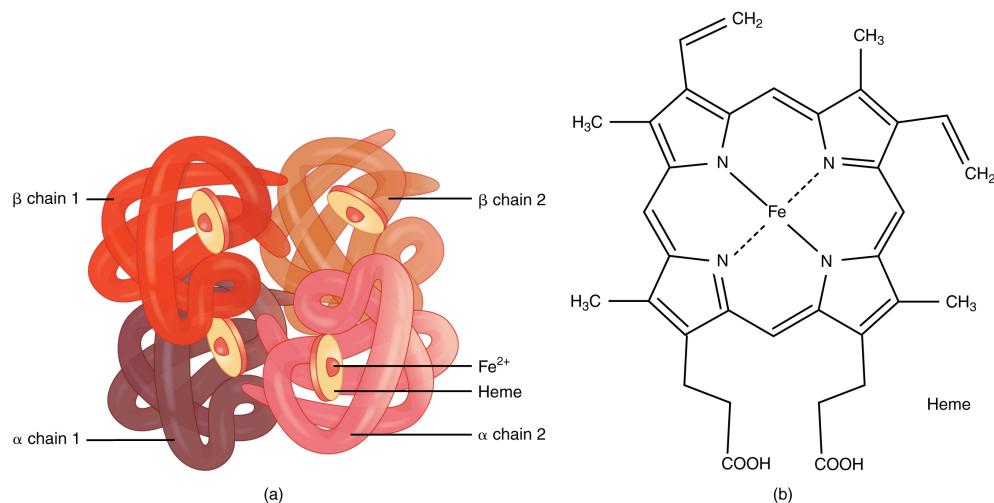


**FIGURE 18.6** Shape of Red Blood Cells Erythrocytes are biconcave discs with very shallow centers. This shape optimizes the ratio of surface area to volume, facilitating gas exchange. It also enables them to fold up as they move through narrow blood vessels.

### 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 18.7a). Each of these globin molecules is bound to a red pigment molecule called **heme**, which contains an ion of iron ( $\text{Fe}^{2+}$ ) (Figure 18.7b).



**FIGURE 18.7 Hemoglobin** (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 18.7b).

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  $\text{CO}_2$ , 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  $\text{P}_{\text{O}_2}$  or  $\text{PO}_2$  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 erythrocytes 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  $\text{Fe}^{2+}$  to  $\text{Fe}^{3+}$ , 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.

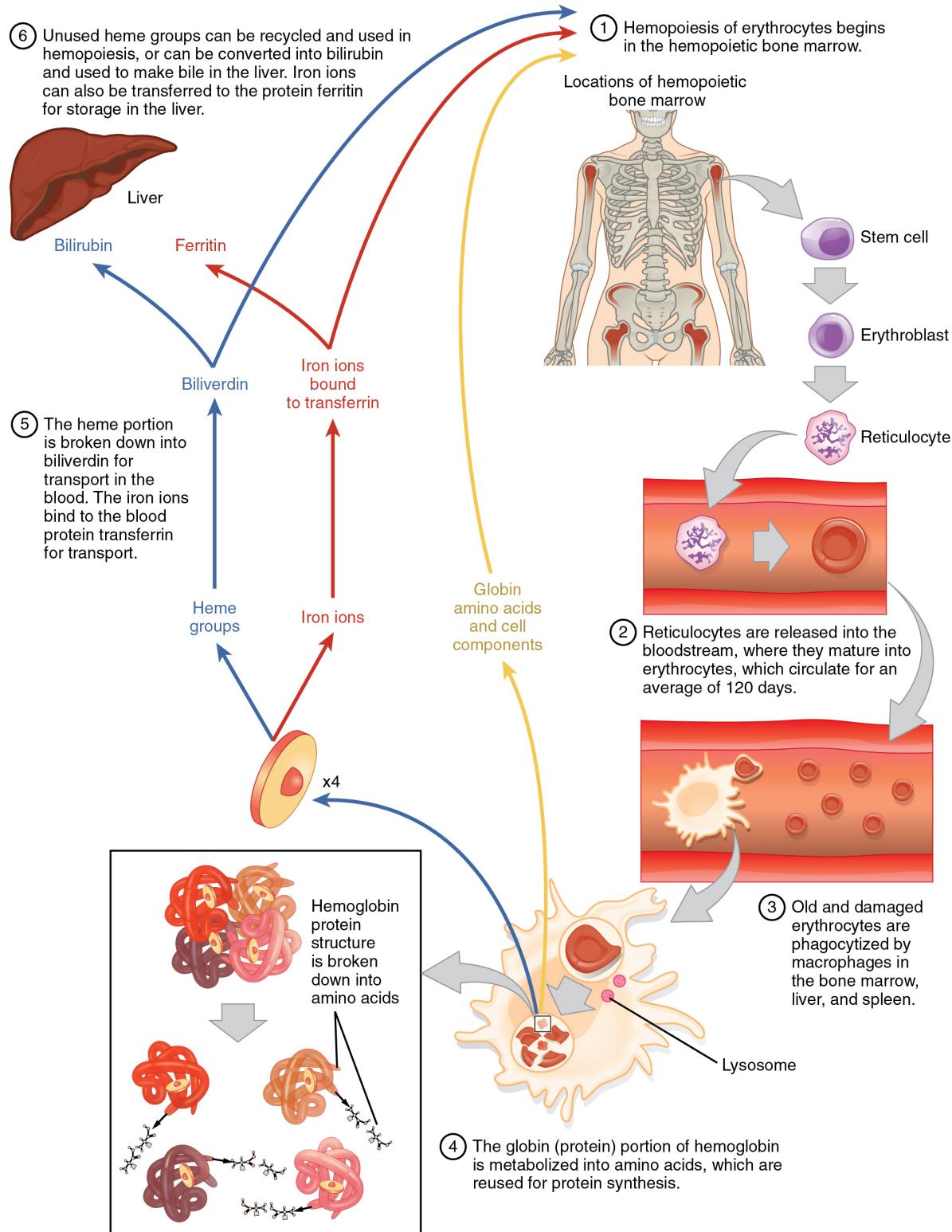
Erythrocytes live up to 120 days in the circulation, after which the worn-out cells are removed by a type of myeloid phagocytic cell called a **macrophage**, located primarily within the bone marrow, liver, and spleen. The components of the degraded erythrocytes' hemoglobin are further processed as follows:

- 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 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 a **bruise**. 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 18.8](#).



**FIGURE 18.8 Erythrocyte Lifecycle** 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

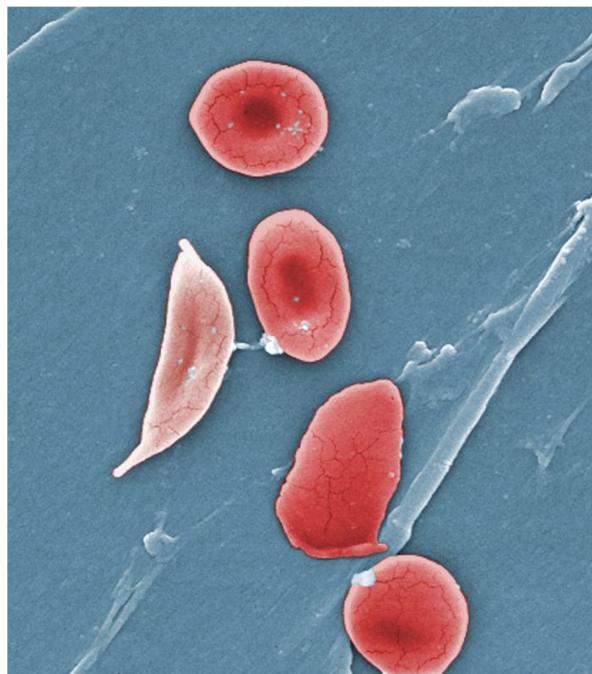
The size, shape, and number of erythrocytes, and the number of hemoglobin molecules can have a major impact on a person's health. When the number of RBCs or hemoglobin is deficient, the general condition is called **anemia**. There are more than 400 types of anemia and more than 3.5 million Americans 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 18.9](#)). 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.



**FIGURE 18.9 Sickle Cells** Sickle cell anemia is caused by a mutation in one of the hemoglobin genes. Erythrocytes produce an abnormal type of hemoglobin, which causes the cell to take on a sickle or crescent shape. (credit: Janice Haney Carr)

- 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 males than in females, and is more likely to be present in elderly patients those over 60 years of age.

## 18.4 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 18.5](#) for a summary of leukocytes and platelets.

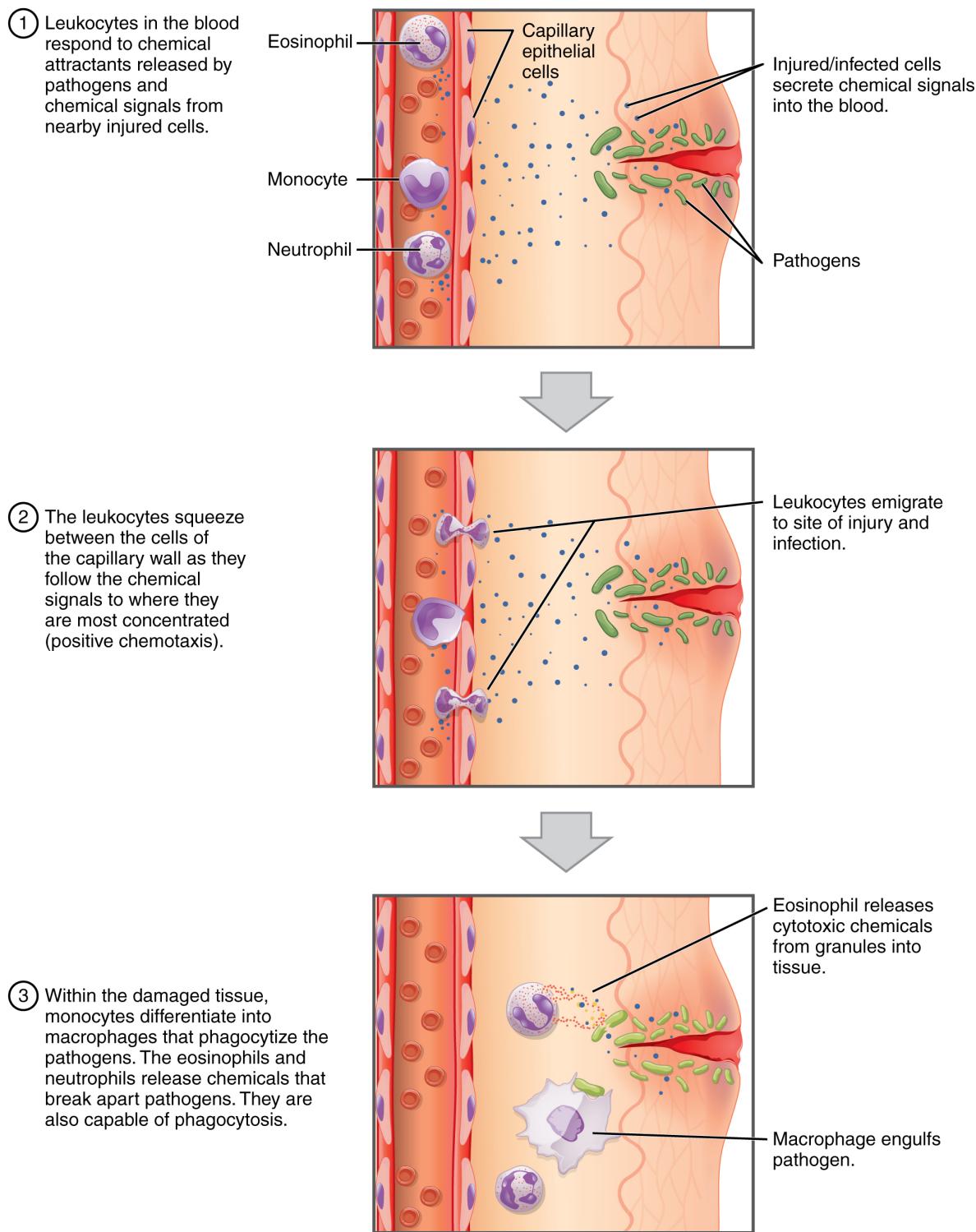
### Characteristics of Leukocytes

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  $\mu\text{L}$ . 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 18.10](#), 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.

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.



**FIGURE 18.10 Emigration** 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.

### 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:

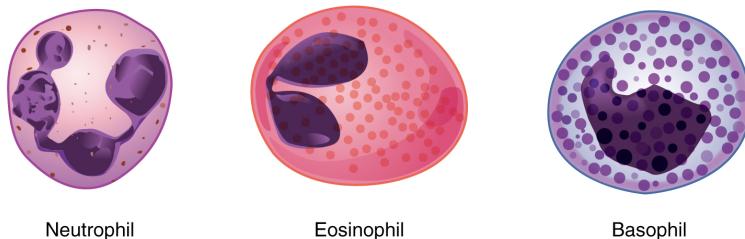
- **Granular leukocytes** contain abundant granules within the cytoplasm. They include neutrophils, eosinophils,

and basophils (you can view their lineage from myeloid stem cells in [Figure 18.4](#)).

- 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 18.11](#)).



**FIGURE 18.11 Granular Leukocytes** 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  $\mu\text{m}$  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  $\mu\text{m}$  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  $\mu\text{m}$  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.

### Agranular Leukocytes

Agranular leukocytes 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 18.4](#)).

**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

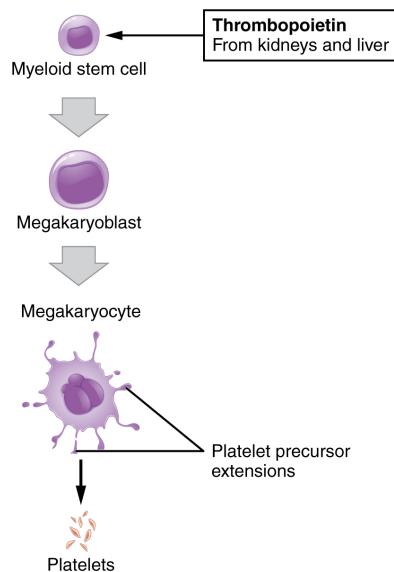
You may occasionally see platelets referred to as **thrombocytes**, but because this name suggests they are a type of cell, it is not accurate. A platelet is not a cell but rather a fragment of the cytoplasm of a cell called a **megakaryocyte** that is surrounded by a plasma membrane. Megakaryocytes are descended from myeloid stem cells (see [Figure 18.4](#)) and are large, typically 50–100  $\mu\text{m}$  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. These remain within bone marrow tissue ([Figure 18.12](#)) 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  $\mu\text{m}$  in diameter, but numerous, with typically 150,000–160,000 per  $\mu\text{L}$  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.

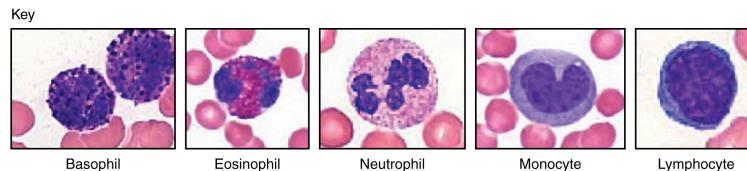
### Disorders of Platelets

**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.



**FIGURE 18.12 Platelets** Platelets are derived from cells called megakaryocytes.

### INTERACTIVE LINK



**FIGURE 18.13 Leukocytes** (Micrographs provided by the Regents of University of Michigan Medical School © 2012)

View [University of Michigan Webscopes \(\*https://openstax.org/r/bloodsmear\*\)](https://openstax.org/r/bloodsmear) 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 in 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?

## 18.5 Hemostasis

### LEARNING OBJECTIVES

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

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

Platelets are key players in **hemostasis**, the process by which the body seals a ruptured blood vessel and prevents further loss of blood. Although rupture of larger vessels usually requires medical intervention, hemostasis is quite effective in dealing with small, simple wounds. There are three steps to the process: vascular spasm, the formation of a platelet plug, and coagulation (blood clotting). Failure of any of these steps will result in **hemorrhage**—excessive bleeding.

## Vascular Spasm

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

## Formation of the Platelet Plug

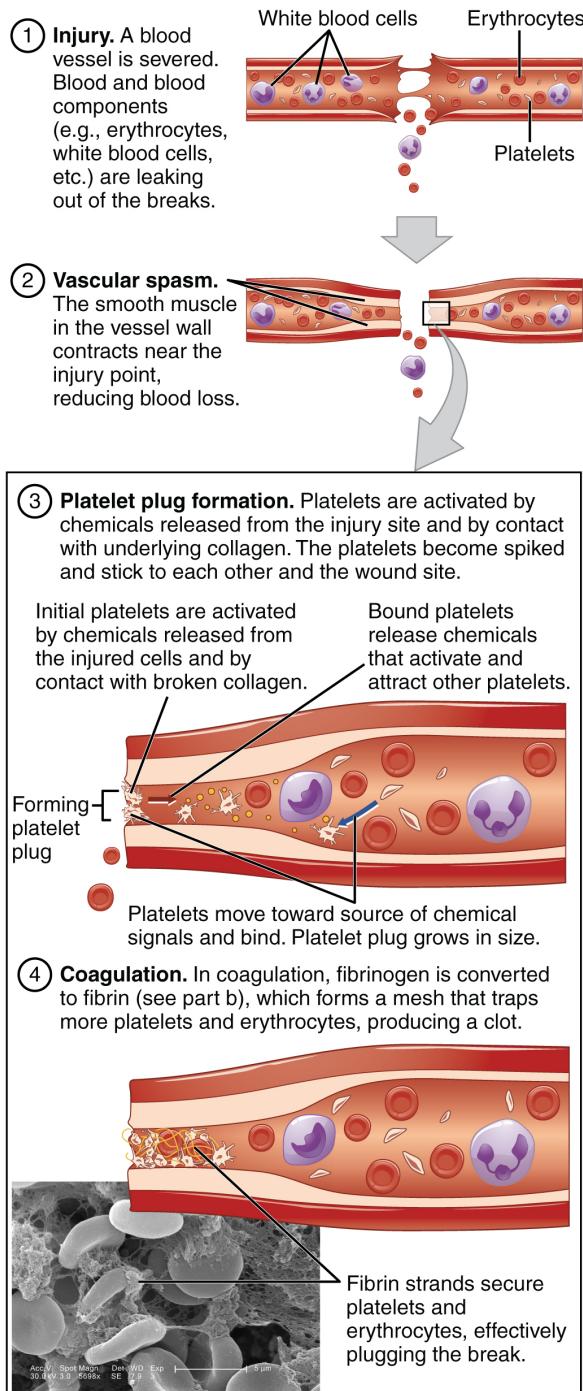
In the second step, platelets, which normally float free in the plasma, encounter the area of vessel rupture with the exposed underlying connective tissue and collagenous fibers. The platelets begin to clump together, become spiked and sticky, and bind to the exposed collagen and endothelial lining.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

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

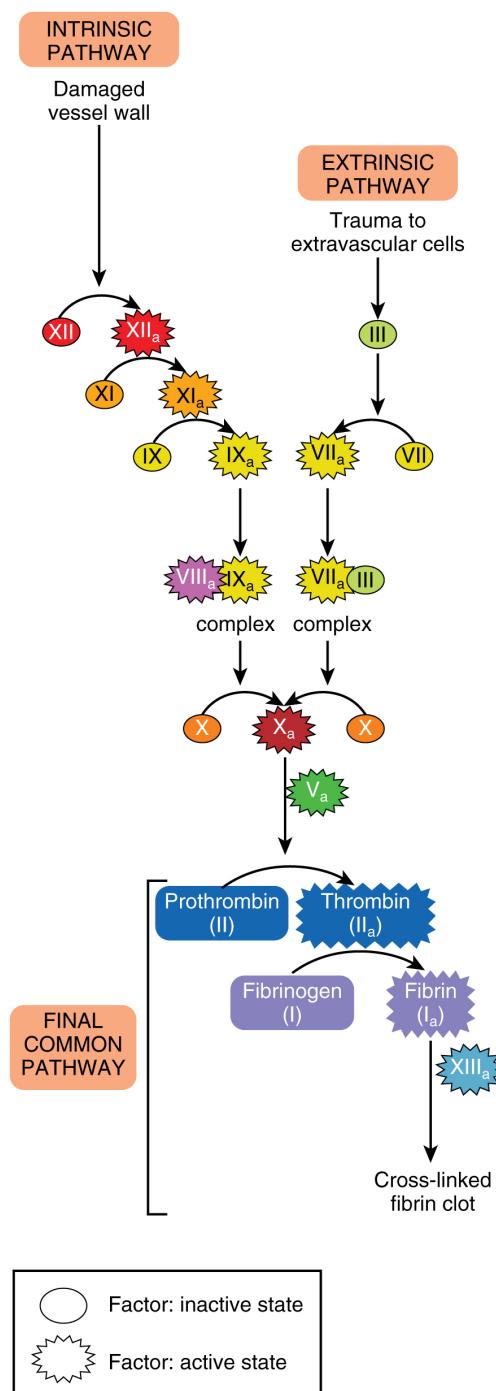
A platelet plug can temporarily seal a small opening in a blood vessel. Plug formation, in essence, buys the body time while more sophisticated and durable repairs are being made. In a similar manner, even modern naval warships still carry an assortment of wooden plugs to temporarily repair small breaches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

## Coagulation

Those more sophisticated and more durable repairs are collectively called **coagulation**, the formation of a blood clot. The process is sometimes characterized as a cascade, because one event prompts the next as in a multi-level waterfall. The result is the production of a gelatinous but robust clot made up of a mesh of **fibrin**—an insoluble filamentous protein derived from fibrinogen, the plasma protein introduced earlier—in which platelets and blood cells are trapped. [Figure 18.14](#) summarizes the three steps of hemostasis.



(a) The general steps of clotting



(b) Fibrin synthesis cascade

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

### Clotting Factors Involved in Coagulation

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

- The extrinsic pathway, which normally is triggered by trauma.
- The intrinsic pathway, which begins in the bloodstream and is triggered by internal damage to the wall of the vessel.

Both of these merge into a third pathway, referred to as the common pathway (see [Figure 18.14b](#)). All three pathways are dependent upon the 12 known clotting factors, including  $\text{Ca}^{2+}$  and vitamin K ([Table 18.1](#)). Clotting factors are secreted primarily by the liver and the platelets. The liver requires the fat-soluble vitamin K to produce many of them. Vitamin K (along with biotin and folate) is somewhat unusual among vitamins in that it is not only consumed in the diet but is also synthesized by bacteria residing in the large intestine. The calcium ion, considered factor IV, is derived from the diet and from the breakdown of bone. Some recent evidence indicates that activation of various clotting factors occurs on specific receptor sites on the surfaces of platelets.

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

#### Clotting Factors

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

**TABLE 18.1** \*Vitamin K required.

Factor number	Name	Type of molecule	Source	Pathway(s)
XII	Hageman factor	Plasma protein	Liver	Intrinsic; initiates clotting in vitro also activates plasmin
XIII	Fibrin-stabilizing factor	Plasma protein	Liver, platelets	Stabilizes fibrin; slows fibrinolysis

**TABLE 18.1** \*Vitamin K required.

#### Extrinsic Pathway

The quicker responding and more direct **extrinsic pathway** (also known as the **tissue factor** pathway) begins when damage occurs to the surrounding tissues, such as in a traumatic injury. Upon contact with blood plasma, the damaged extravascular cells, which are extrinsic to the bloodstream, release factor III (thromboplastin). Sequentially,  $\text{Ca}^{2+}$  then factor VII (proconvertin), which is activated by factor III, are added, forming an enzyme complex. This enzyme complex leads to activation of factor X (Stuart–Prower factor), which activates the common pathway discussed below. The events in the extrinsic pathway are completed in a matter of seconds.

#### Intrinsic Pathway

The **intrinsic pathway** (also known as the contact activation pathway) is longer and more complex. In this case, the factors involved are intrinsic to (present within) the bloodstream. The pathway can be prompted by damage to the tissues, resulting from internal factors such as arterial disease; however, it is most often initiated when factor XII (Hageman factor) comes into contact with foreign materials, such as when a blood sample is put into a glass test tube. Within the body, factor XII is typically activated when it encounters negatively charged molecules, such as inorganic polymers and phosphate produced earlier in the series of intrinsic pathway reactions. Factor XII sets off a series of reactions that in turn activates factor XI (antihemolytic factor C or plasma thromboplastin antecedent) then factor IX (antihemolytic factor B or plasma thromboplastin). In the meantime, chemicals released by the platelets increase the rate of these activation reactions. Finally, factor VIII (antihemolytic factor A) from the platelets and endothelial cells combines with factor IX (antihemolytic factor B or plasma thromboplastin) to form an enzyme complex that activates factor X (Stuart–Prower factor or thrombokinase), leading to the common pathway. The events in the intrinsic pathway are completed in a few minutes.

#### Common Pathway

Both the intrinsic and extrinsic pathways lead to the **common pathway**, in which fibrin is produced to seal off the vessel. Once factor X has been activated by either the intrinsic or extrinsic pathway, the enzyme prothrombinase converts factor II, the inactive enzyme prothrombin, into the active enzyme **thrombin**. (Note that if the enzyme thrombin were not normally in an inactive form, clots would form spontaneously, a condition not consistent with life.) Then, thrombin converts factor I, the soluble fibrinogen, into the insoluble fibrin protein strands. Factor XIII then stabilizes the fibrin clot.

#### Fibrinolysis

The stabilized clot is acted upon by contractile proteins within the platelets. As these proteins contract, they pull on the fibrin threads, bringing the edges of the clot more tightly together, somewhat as we do when tightening loose shoelaces (see [Figure 18.14a](#)). This process also wrings out of the clot a small amount of fluid called **serum**, which is blood plasma without its clotting factors.

To restore normal blood flow as the vessel heals, the clot must eventually be removed. **Fibrinolysis** is the gradual degradation of the clot. Again, there is a fairly complicated series of reactions that involves factor XII and protein-catabolizing enzymes. During this process, the inactive protein plasminogen is converted into the active **plasmin**, which gradually breaks down the fibrin of the clot. Additionally, bradykinin, a vasodilator, is released, reversing the effects of the serotonin and prostaglandins from the platelets. This allows the smooth muscle in the walls of the vessels to relax and helps to restore the circulation.

## Plasma Anticoagulants

An **anticoagulant** is any substance that opposes coagulation. Several circulating plasma anticoagulants play a role in limiting the coagulation process to the region of injury and restoring a normal, clot-free condition of blood. For instance, a cluster of proteins collectively referred to as the protein C system inactivates clotting factors involved in the intrinsic pathway. TFPI (tissue factor pathway inhibitor) inhibits the conversion of the inactive factor VII to the active form in the extrinsic pathway. **Antithrombin** inactivates factor X and opposes the conversion of prothrombin (factor II) to thrombin in the common pathway. And as noted earlier, basophils release **heparin**, a short-acting anticoagulant that also opposes prothrombin. Heparin is also found on the surfaces of cells lining the blood vessels. A pharmaceutical form of heparin is often administered therapeutically, for example, in surgical patients at risk for blood clots.

### INTERACTIVE LINK

View these [animations](http://openstax.org/l/coagulation) (<http://openstax.org/l/coagulation>) to explore the intrinsic, extrinsic, and common pathways that are involved the process of coagulation. The coagulation cascade restores hemostasis by activating coagulation factors in the presence of an injury. How does the endothelium of the blood vessel walls prevent the blood from coagulating as it flows through the blood vessels?

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## Disorders of Clotting

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

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

In contrast to the disorders characterized by coagulation failure is thrombocytosis, also mentioned earlier, a condition characterized by excessive numbers of platelets that increases the risk for excessive clot formation, a condition known as **thrombosis**. A **thrombus** (plural = *thrombi*) is an aggregation of platelets, erythrocytes, and even WBCs typically trapped within a mass of fibrin strands. While the formation of a clot is normal following the hemostatic mechanism just described, thrombi can form within an intact or only slightly damaged blood vessel. In a large vessel, a thrombus will adhere to the vessel wall and decrease the flow of blood, and is referred to as a mural thrombus. In a small vessel, it may actually totally block the flow of blood and is termed an occlusive thrombus. Thrombi are most commonly caused by vessel damage to the endothelial lining, which activates the clotting mechanism. These may include venous stasis, when blood in the veins, particularly in the legs, remains stationary for long periods. This is one of the dangers of long airplane flights in crowded conditions and may lead to deep vein thrombosis. Thrombophilia, also called hypercoagulation, is a condition in which there is a tendency to form thrombosis. This may be familial (genetic) or acquired. Acquired forms include the autoimmune disease lupus, immune reactions to heparin, polycythemia vera, thrombocytosis, sickle cell disease, pregnancy, and even obesity. A thrombus can seriously impede blood flow to or from a region and will cause a local increase in blood pressure. If flow is to be maintained, the heart will need to generate a greater pressure to overcome the resistance.

When a portion of a thrombus breaks free from the vessel wall and enters the circulation, it is referred to as an

**embolus.** An embolus that is carried through the bloodstream can be large enough to block a vessel critical to a major organ. When it becomes trapped, an embolus is called an embolism. In the heart, brain, or lungs, an embolism may accordingly cause a heart attack, a stroke, or a pulmonary embolism. These are medical emergencies.

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

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

## 18.6 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.

The body must be exposed to a foreign antigen before an antibody can be produced. ABO blood group antigens are found in foods and microbes throughout nature. Thus, the human immune system is exposed to A and B antigens at an early age and antibodies are formed naturally. Individuals with type A blood—without any prior exposure to incompatible blood—have naturally-formed antibodies to the B antigen circulating in their blood plasma. These antibodies, referred to as anti-B antibodies, will cause agglutination and hemolysis if they ever encounter erythrocytes with B antigens. Similarly, an individual with type B blood has naturally-formed anti-A antibodies. Individuals with type AB blood, which has both antigens, do not have naturally-formed antibodies to either of these. People with type O blood lack antigens A and B on their erythrocytes, but both anti-A and anti-B antibodies circulate in their blood plasma.

### Rh Blood Groups

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

[Table 18.2](#) summarizes the distribution of the ABO and Rh blood types within the United States.

**Summary of ABO and Rh Blood Types within the United States**

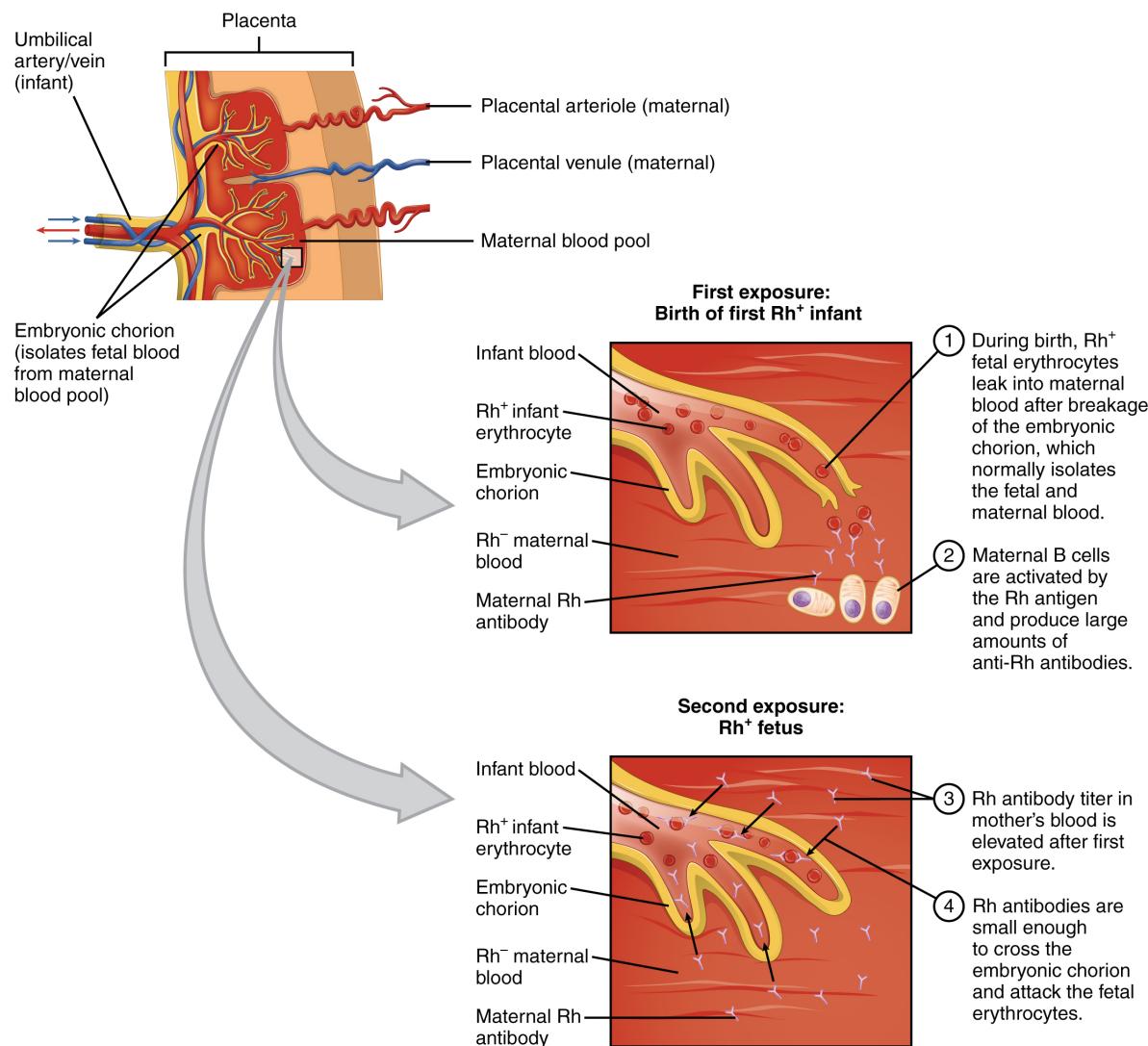
Blood Type	Asian	Black non-Hispanic	Hispanic	North American Indian	White non-Hispanic
A <sup>+</sup>	27.3	24.0	28.7	31.3	33.0
A <sup>-</sup>	0.5	1.9	2.4	3.8	6.8
B <sup>+</sup>	25.0	18.4	9.2	7.0	9.1
B <sup>-</sup>	0.4	1.3	0.7	0.9	1.8
AB <sup>+</sup>	7.0	4.0	2.3	2.2	3.4
AB <sup>-</sup>	0.1	0.3	0.2	0.3	0.7

**TABLE 18.2**

Blood Type	Asian	Black non-Hispanic	Hispanic	North American Indian	White non-Hispanic
O <sup>+</sup>	39.0	46.6	52.6	50.0	37.2
O <sup>-</sup>	0.7	3.6	3.9	4.7	8.0

**TABLE 18.2**

In contrast to the ABO group antibodies, which are preformed, antibodies to the Rh antigen are produced only in Rh<sup>-</sup> 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<sup>+</sup> baby to an Rh<sup>-</sup> person. Problems are rare in a first pregnancy, since the baby's Rh<sup>+</sup> cells rarely cross the placenta (the organ of gas and nutrient exchange between the fetus and the pregnant person). However, during or immediately after birth, the Rh<sup>-</sup> parent can be exposed to the baby's Rh<sup>+</sup> cells (Figure 18.15). Research has shown that this occurs in about 13–14 percent of such pregnancies. After exposure, the immune system of the person who has given birth begins to generate anti-Rh antibodies. If the same person should then become pregnant with another Rh<sup>+</sup> baby, the Rh antibodies they have produced can cross the placenta into the fetal bloodstream and destroy the fetal RBCs. This condition, known as **hemolytic disease of the newborn (HDN)** or erythroblastosis fetalis, may cause anemia in mild cases, but the agglutination and hemolysis can be so severe that without treatment the fetus may die in the womb or shortly after birth.

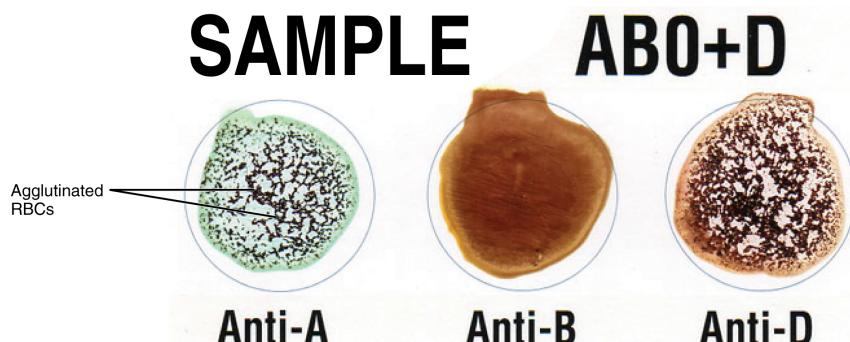
**FIGURE 18.15 Erythroblastosis Fetalis** The first exposure of an Rh<sup>-</sup> person to Rh<sup>+</sup> erythrocytes during pregnancy induces

sensitization. Anti-Rh antibodies begin to circulate in the pregnant person's bloodstream. A second exposure occurs with a subsequent pregnancy with an Rh<sup>+</sup> fetus in the uterus. During that subsequent pregnancy, the pregnant person's anti-Rh antibodies may cross the placenta and enter the fetal bloodstream, causing agglutination and hemolysis of fetal erythrocytes.

A drug known as RhoGAM, short for Rh immune globulin, can temporarily prevent the development of Rh antibodies in the Rh<sup>-</sup> parent, thereby averting this potentially serious disease for the fetus. RhoGAM antibodies destroy any fetal Rh<sup>+</sup> erythrocytes that may cross the placental barrier. RhoGAM is normally administered to Rh<sup>-</sup> pregnant people during weeks 26–28 of pregnancy and within 72 hours following birth. It has proven remarkably effective in decreasing the incidence of HDN. Earlier we noted that the incidence of HDN in an Rh<sup>+</sup> subsequent pregnancy to an Rh<sup>-</sup> person 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 18.16). The blood should also be tested for Rh antibodies.



**FIGURE 18.16 Cross Matching Blood Types** 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<sup>+</sup>. 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<sup>+</sup> recipient should ideally receive blood only from a type B<sup>+</sup> 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<sup>-</sup> 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<sup>-</sup> 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 effects of the relatively few infused plasma antibodies are typically limited. Rh factor also plays a role. If Rh<sup>-</sup> 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<sup>+</sup> 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<sup>+</sup> patient can receive both Rh<sup>+</sup> and Rh<sup>-</sup> blood. However, keep in mind that the donor’s blood will contain circulating antibodies, again with possible negative implications. Figure 18.17 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.

	Blood Type			
	A	B	AB	O
Red Blood Cell Type				
Antibodies in Plasma			None	
Antigens in Red blood Cell	A antigen	B antigen	A and B antigens	None
Blood Types Compatible in an Emergency	A, O	B, O	A, B, AB, O (AB <sup>+</sup> is the universal recipient)	O (O is the universal donor)

**FIGURE 18.17 ABO Blood Group** 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.

## Key Terms

- 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
- agranular leukocytes** leukocytes with few granules in their cytoplasm; specifically, monocytes, lymphocytes, and NK cells
- albumin** most abundant plasma protein, accounting for most of the osmotic pressure of plasma
- anemia** deficiency of red blood cells or hemoglobin
- 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
- anticoagulant** substance such as heparin that opposes coagulation
- antithrombin** anticoagulant that inactivates factor X and opposes the conversion of prothrombin (factor II) into thrombin in the common pathway
- 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
- 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
- blood** liquid connective tissue composed of formed elements—erythrocytes, leukocytes, and platelets—and a fluid extracellular matrix called plasma; component of the cardiovascular system
- bone marrow biopsy** diagnostic test of a sample of red bone marrow
- bone marrow transplant** treatment in which a donor's healthy bone marrow with its stem cells replaces diseased or damaged bone marrow of a patient
- bruise** localized bleeding under the skin due to damaged blood vessels
- buffy coat** thin, pale layer of leukocytes and platelets that separates the erythrocytes from the plasma in a sample of centrifuged blood
- carbaminohemoglobin** compound of carbon dioxide and hemoglobin, and one of the ways in which carbon dioxide is carried in the blood
- clotting factors** group of 12 identified substances active in coagulation
- coagulation** formation of a blood clot; part of the process of hemostasis
- colony-stimulating factors (CSFs)** glycoproteins that trigger the proliferation and differentiation of myeloblasts into granular leukocytes (basophils, neutrophils, and eosinophils)
- common pathway** final coagulation pathway activated either by the intrinsic or the extrinsic pathway, and ending in the formation of a blood clot
- cross matching** blood test for identification of blood type using antibodies and small samples of blood
- cytokines** class of proteins that act as autocrine or paracrine signaling molecules; in the cardiovascular system, they stimulate the proliferation of progenitor cells and help to stimulate both nonspecific and specific resistance to disease
- defensins** antimicrobial proteins released from neutrophils and macrophages that create openings in the plasma membranes to kill cells
- deoxyhemoglobin** molecule of hemoglobin without an oxygen molecule bound to it
- diapedesis** (also, emigration) process by which leukocytes squeeze through adjacent cells in a blood vessel wall to enter tissues
- embolus** thrombus that has broken free from the blood vessel wall and entered the circulation
- 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
- 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
- erythropoietin (EPO)** glycoprotein that triggers the bone marrow to produce RBCs; secreted by the kidney in response to low oxygen levels
- extrinsic pathway** initial coagulation pathway that begins with tissue damage and results in the activation of the common pathway
- ferritin** protein-containing storage form of iron found in the bone marrow, liver, and spleen
- fibrin** insoluble, filamentous protein that forms the structure of a blood clot
- fibrinogen** plasma protein produced in the liver and involved in blood clotting
- fibrinolysis** gradual degradation of a blood clot
- formed elements** cellular components of blood; that is, erythrocytes, leukocytes, and platelets
- globin** heme-containing globular protein that is a

- constituent of hemoglobin
- globulins** heterogeneous group of plasma proteins that includes transport proteins, clotting factors, immune proteins, and others
- granular leukocytes** leukocytes with abundant granules in their cytoplasm; specifically, neutrophils, eosinophils, and basophils
- hematocrit** (also, packed cell volume) volume percentage of erythrocytes in a sample of centrifuged blood
- hematopoietic stem cell** type of pluripotent stem cell that gives rise to the formed elements of blood (hemocytoblast)
- heme** red, iron-containing pigment to which oxygen binds in hemoglobin
- hemocytoblast** hematopoietic stem cell that gives rise to the formed elements of blood
- hemoglobin** oxygen-carrying compound in erythrocytes
- 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<sup>+</sup> fetus or newborn of an Rh<sup>-</sup> person
- hemophilia** genetic disorder characterized by inadequate synthesis of clotting factors
- hemopoiesis** production of the formed elements of blood
- hemopoietic growth factors** chemical signals including erythropoietin, thrombopoietin, colony-stimulating factors, and interleukins that regulate the differentiation and proliferation of particular blood progenitor cells
- hemorrhage** excessive bleeding
- hemosiderin** protein-containing storage form of iron found in the bone marrow, liver, and spleen
- hemostasis** physiological process by which bleeding ceases
- heparin** short-acting anticoagulant stored in mast cells and released when tissues are injured, opposes prothrombin
- hypoxemia** below-normal level of oxygen saturation of blood (typically <95 percent)
- 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
- interleukins** signaling molecules that may function in hemopoiesis, inflammation, and specific immune responses
- intrinsic pathway** initial coagulation pathway that begins with vascular damage or contact with foreign substances, and results in the activation of the common pathway
- jaundice** yellowing of the skin or whites of the eyes due to excess bilirubin in the blood
- 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
- lymphoid stem cells** type of hematopoietic stem cells that gives rise to lymphocytes, including various T cells, B cells, and NK cells, all of which function in 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
- macrophage** phagocytic cell of the myeloid lineage; a matured monocyte
- 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
- myeloid stem cells** type of hematopoietic stem cell that gives rise to some formed elements, including erythrocytes, megakaryocytes that produce platelets, and a myeloblast lineage that gives rise to monocytes and three forms of granular leukocytes (neutrophils, eosinophils, and basophils)
- 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
- oxyhemoglobin** molecule of hemoglobin to which oxygen is bound
- 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	leading to abnormal formation of hemoglobin and the destruction of RBCs
<b>plasmin</b> blood protein active in fibrinolysis	<b>thrombin</b> enzyme essential for the final steps in formation of a fibrin clot
<b>platelet plug</b> accumulation and adhesion of platelets at the site of blood vessel injury	<b>thrombocytes</b> platelets, one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes
<b>platelets</b> (also, thrombocytes) one of the formed elements of blood that consists of cell fragments broken off from megakaryocytes	<b>thrombocytopenia</b> condition in which there are too few platelets, resulting in abnormal bleeding (hemophilia)
<b>pluripotent stem cell</b> stem cell that derives from totipotent stem cells and is capable of differentiating into many, but not all, cell types	<b>thrombocytosis</b> condition in which there are too many platelets, resulting in abnormal clotting (thrombosis)
<b>polycythemia</b> elevated level of hemoglobin, whether adaptive or pathological	<b>thrombopoietin</b> hormone secreted by the liver and kidneys that prompts the development of megakaryocytes into thrombocytes (platelets)
<b>polymorphonuclear</b> having a lobed nucleus, as seen in some leukocytes	<b>thrombosis</b> excessive clot formation
<b>positive chemotaxis</b> process in which a cell is attracted to move in the direction of chemical stimuli	<b>thrombus</b> aggregation of fibrin, platelets, and erythrocytes in an intact artery or vein
<b>red blood cells (RBCs)</b> (also, erythrocytes) one of the formed elements of blood that transports oxygen	<b>tissue factor</b> protein thromboplastin, which initiates the extrinsic pathway when released in response to tissue damage
<b>reticulocyte</b> immature erythrocyte that may still contain fragments of organelles	<b>totipotent stem cell</b> embryonic stem cell that is capable of differentiating into any and all cells of the body; enabling the full development of an organism
<b>Rh blood group</b> blood-type classification based on the presence or absence of the antigen Rh on the erythrocyte membrane surface	<b>transferrin</b> plasma protein that binds reversibly to iron and distributes it throughout the body
<b>serum</b> blood plasma that does not contain clotting factors	<b>universal donor</b> individual with type O <sup>-</sup> blood
<b>sickle cell disease</b> (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	<b>universal recipient</b> individual with type AB <sup>+</sup> blood
<b>T lymphocytes</b> (also, T cells) lymphocytes that provide cellular-level immunity by physically attacking foreign or diseased cells	<b>vascular spasm</b> initial step in hemostasis, in which the smooth muscle in the walls of the ruptured or damaged blood vessel contracts
<b>thalassemia</b> inherited blood disorder in which maturation of RBCs does not proceed normally,	<b>white blood cells (WBCs)</b> (also, leukocytes) one of the formed elements of blood that provides defense against disease agents and foreign materials

## Chapter Review

### 18.1 An Overview of Blood

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.

### 18.2 Production of the Formed Elements

Through the process of hemopoiesis, the formed elements of blood are continually produced, replacing the relatively short-lived erythrocytes, leukocytes, and platelets. Hemopoiesis begins in the red bone marrow, with hematopoietic stem cells that differentiate into myeloid and lymphoid lineages. Myeloid stem cells give rise to most of the formed elements. Lymphoid stem cells give rise only to the various lymphocytes designated as B and T cells, and NK cells. Hemopoietic growth factors, including erythropoietin,

thrombopoietin, colony-stimulating factors, and interleukins, promote the proliferation and differentiation of formed elements.

### 18.3 Erythrocytes

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.

### 18.4 Leukocytes and Platelets

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.

### 18.5 Hemostasis

Hemostasis is the physiological process by which bleeding ceases. Hemostasis involves three basic steps: vascular spasm, the formation of a platelet plug, and coagulation, in which clotting factors promote the formation of a fibrin clot. Fibrinolysis is the process in which a clot is degraded in a healing vessel.

Anticoagulants are substances that oppose coagulation. They are important in limiting the extent and duration of clotting. Inadequate clotting can result from too few platelets, or inadequate production of clotting factors, for instance, in the genetic disorder hemophilia. Excessive clotting, called thrombosis, can be caused by excessive numbers of platelets. A thrombus is a collection of fibrin, platelets, and erythrocytes that has accumulated along the lining of a blood vessel, whereas an embolus is a thrombus that has broken free from the vessel wall and is circulating in the bloodstream.

### 18.6 Blood Typing

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<sup>-</sup> blood do not have this antigen on their erythrocytes, whereas those who are Rh<sup>+</sup> do. About 85 percent of Americans are Rh<sup>+</sup>. When a person who is Rh<sup>-</sup> becomes pregnant with an Rh<sup>+</sup> fetus, their body may begin to produce anti-Rh antibodies. If the person subsequently becomes pregnant with a second Rh<sup>+</sup> 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<sup>-</sup> blood may be transfused.

## Interactive Link Questions

1. Visit this [site](http://openstax.org/l/normallevels) (<http://openstax.org/l/normallevels>) 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?
2. Watch this [video](http://openstax.org/l/doping) (<http://openstax.org/l/doping>) to see doctors discuss the dangers of blood doping in sports. What are some potential side effects of blood doping?
3. [Figure 18.13](#) Are you able to recognize and identify the various formed elements? You will need to do this in 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?
4. View these [animations](#) (<http://openstax.org/l/coagulation>) to explore the intrinsic, extrinsic, and common pathways that are involved in the process of coagulation. The coagulation cascade restores hemostasis by activating coagulation factors in the presence of an injury. How does the endothelium of the blood vessel walls prevent the blood from coagulating as it flows through the blood vessels?

## Review Questions

5. Which of the following statements about blood is true?
  - a. Blood is about 92 percent water.
  - b. Blood is slightly more acidic than water.
  - c. Blood is slightly more viscous than water.
  - d. Blood is slightly more salty than seawater.
6. Which of the following statements about albumin is true?
  - a. It draws water out of the blood vessels and into the body's tissues.
  - b. It is the most abundant plasma protein.
  - c. It is produced by specialized leukocytes called plasma cells.
  - d. All of the above are true.
7. Which of the following plasma proteins is *not* produced by the liver?
  - a. fibrinogen
  - b. alpha globulin
  - c. beta globulin
  - d. immunoglobulin
8. Which of the formed elements arise from myeloid stem cells?
  - a. B cells
  - b. natural killer cells
  - c. platelets
  - d. all of the above
9. Which of the following statements about erythropoietin is true?
  - a. It facilitates the proliferation and differentiation of the erythrocyte lineage.
  - b. It is a hormone produced by the thyroid gland.
  - c. It is a hemopoietic growth factor that prompts lymphoid stem cells to leave the bone marrow.
  - d. Both a and b are true.
10. Interleukins are associated primarily with which of the following?
  - a. production of various lymphocytes
  - b. immune responses
  - c. inflammation
  - d. all of the above
11. Which of the following statements about mature, circulating erythrocytes is true?
  - a. They have no nucleus.
  - b. They are packed with mitochondria.
  - c. They survive for an average of 4 days.
  - d. All of the above
12. A molecule of hemoglobin \_\_\_\_\_.
  - a. is shaped like a biconcave disk packed almost entirely with iron
  - b. contains four glycoprotein units studded with oxygen
  - c. consists of four globin proteins, each bound to a molecule of heme
  - d. can carry up to 120 molecules of oxygen

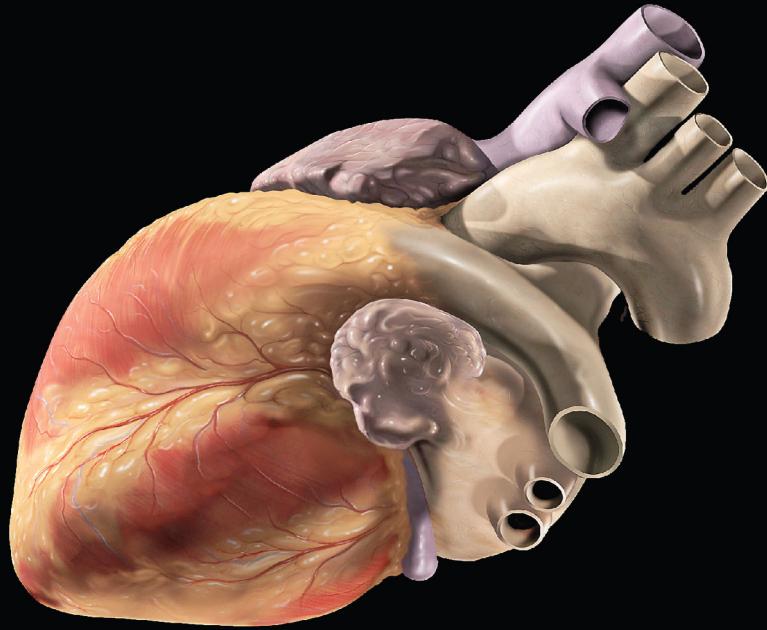
- 13.** The production of healthy erythrocytes depends upon the availability of \_\_\_\_\_.  
 a. copper  
 b. zinc  
 c. vitamin B<sub>12</sub>  
 d. copper, zinc, and vitamin B<sub>12</sub>
- 14.** Aging and damaged erythrocytes are removed from the circulation by \_\_\_\_\_.  
 a. myeoblasts  
 b. monocytes  
 c. macrophages  
 d. mast cells
- 15.** A patient has been suffering for 2 months with a chronic, watery diarrhea. A blood test is likely to reveal \_\_\_\_\_.  
 a. a hematocrit below 30 percent  
 b. hypoxemia  
 c. anemia  
 d. polycythemia
- 16.** The process by which leukocytes squeeze through adjacent cells in a blood vessel wall is called \_\_\_\_\_.  
 a. leukocytosis  
 b. positive chemotaxis  
 c. emigration  
 d. cytoplasmic extending
- 17.** Which of the following describes a neutrophil?  
 a. abundant, agranular, especially effective against cancer cells  
 b. abundant, granular, especially effective against bacteria  
 c. rare, agranular, releases antimicrobial defensins  
 d. rare, granular, contains multiple granules packed with histamine
- 18.** T and B lymphocytes \_\_\_\_\_.  
 a. are polymorphonuclear  
 b. are involved with specific immune function  
 c. proliferate excessively in leukopenia  
 d. are most active against parasitic worms
- 19.** A patient has been experiencing severe, persistent allergy symptoms that are reduced when she takes an antihistamine. Before the treatment, this patient was likely to have had increased activity of which leukocyte?  
 a. basophils  
 b. neutrophils  
 c. monocytes  
 d. natural killer cells
- 20.** Thrombocytes are more accurately called \_\_\_\_\_.  
 a. clotting factors  
 b. megakaryoblasts  
 c. megakaryocytes  
 d. platelets
- 21.** The first step in hemostasis is \_\_\_\_\_.  
 a. vascular spasm  
 b. conversion of fibrinogen to fibrin  
 c. activation of the intrinsic pathway  
 d. activation of the common pathway
- 22.** Prothrombin is converted to thrombin during the \_\_\_\_\_.  
 a. intrinsic pathway  
 b. extrinsic pathway  
 c. common pathway  
 d. formation of the platelet plug
- 23.** Hemophilia is characterized by \_\_\_\_\_.  
 a. inadequate production of heparin  
 b. inadequate production of clotting factors  
 c. excessive production of fibrinogen  
 d. excessive production of platelets
- 24.** The process in which antibodies attach to antigens, causing the formation of masses of linked cells, is called \_\_\_\_\_.  
 a. sensitization  
 b. coagulation  
 c. agglutination  
 d. hemolysis
- 25.** People with ABO blood type O \_\_\_\_\_.  
 a. have both antigens A and B on their erythrocytes  
 b. lack both antigens A and B on their erythrocytes  
 c. have neither anti-A nor anti-B antibodies circulating in their blood plasma  
 d. are considered universal recipients
- 26.** Hemolytic disease of the newborn is a risk during a subsequent pregnancy in which \_\_\_\_\_.  
 a. a type AB person is carrying a type O fetus  
 b. a type O person is carrying a type AB fetus  
 c. an Rh<sup>+</sup> person is carrying an Rh<sup>-</sup> fetus  
 d. an Rh<sup>-</sup> person is carrying a second Rh<sup>+</sup> fetus

## Critical Thinking Questions

- 27.** A patient's hematocrit is 42 percent. Approximately what percentage of the patient's blood is plasma?
- 28.** Why would it be incorrect to refer to the formed elements as cells?
- 29.** True or false: The buffy coat is the portion of a blood sample that is made up of its proteins.
- 30.** Myelofibrosis is a disorder in which inflammation and scar tissue formation in the bone marrow impair hemopoiesis. One sign is an enlarged spleen. Why?
- 31.** Would you expect a patient with a form of cancer called acute myelogenous leukemia to experience impaired production of erythrocytes, or impaired production of lymphocytes? Explain your choice.
- 32.** A young person has been experiencing unusually heavy menstrual bleeding for several years. They follow a strict vegan diet (no animal foods). They are at risk for what disorder, and why?
- 33.** 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 their blood. Explain the connection.
- 34.** 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?
- 35.** A patient was admitted to the burn unit the previous evening suffering from a severe burn involving their left upper extremity and shoulder. A blood test reveals that they are experiencing leukocytosis. Why is this an expected finding?
- 36.** A lab technician collects a blood sample in a glass tube. After about an hour, she harvests serum to continue her blood analysis. Explain what has happened during the hour that the sample was in the glass tube.
- 37.** Explain why administration of a thrombolytic agent is a first intervention for someone who has suffered a thrombotic stroke.
- 38.** 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 their blood type. What type of blood is transfused, and why?
- 39.** 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?

## CHAPTER 19

# The Cardiovascular System: The Heart



**Figure 19.1 Human Heart** 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)

## CHAPTER 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

**INTRODUCTION** 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.

## 19.1 Heart Anatomy

### LEARNING OBJECTIVES

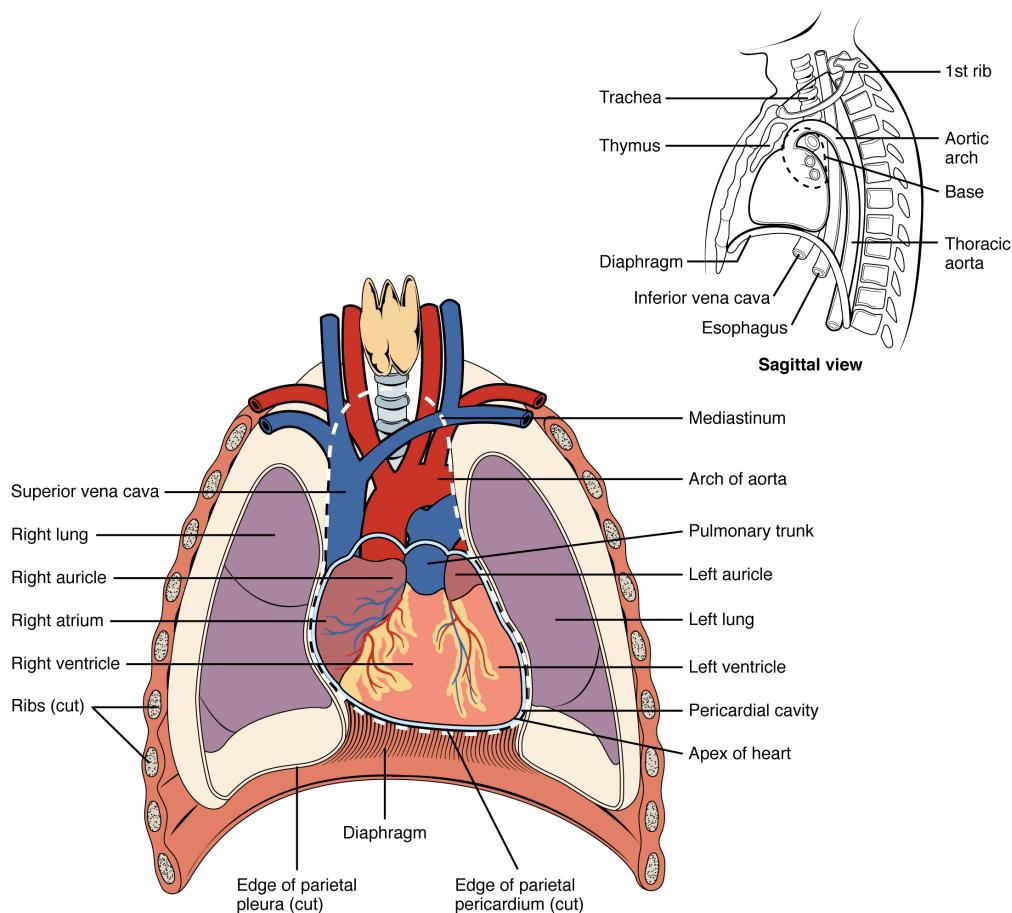
By the end of this section, you will be able to:

- 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 19.2](#) 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 19.2](#). 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 19.2 Position of the Heart in the Thorax** 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.

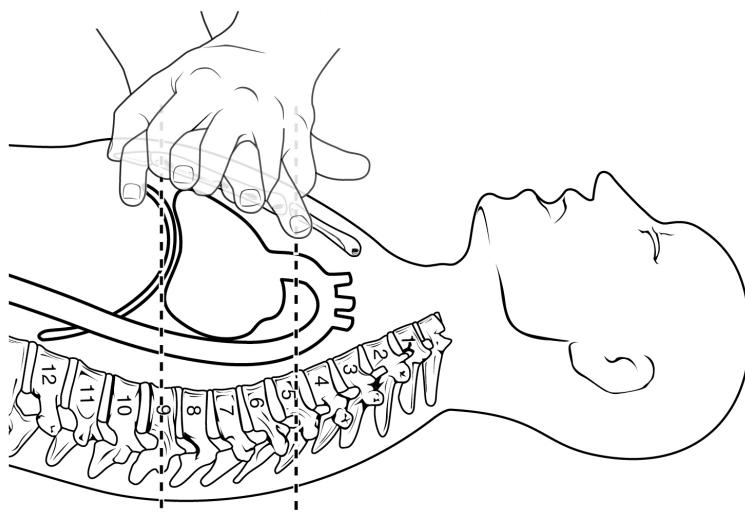
### Everyday Connection

#### CPR

The position of the heart in the torso between the vertebrae and sternum (see [Figure 19.2](#) 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 line at T4 and T9 ([Figure 19.3](#)), 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, a version is available on [www.youtube.com](http://www.youtube.com). 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 patient. 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 19.3 CPR Technique** 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.

### **INTERACTIVE LINK**

Visit the American Heart Association [website \(<http://openstax.org/l/AHA>\)](http://openstax.org/l/AHA) to help locate a course near your home in the United States. There are also many other national and regional heart associations that offer the same service, depending upon the location.

## 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 (see [Figure 19.2](#)). 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.

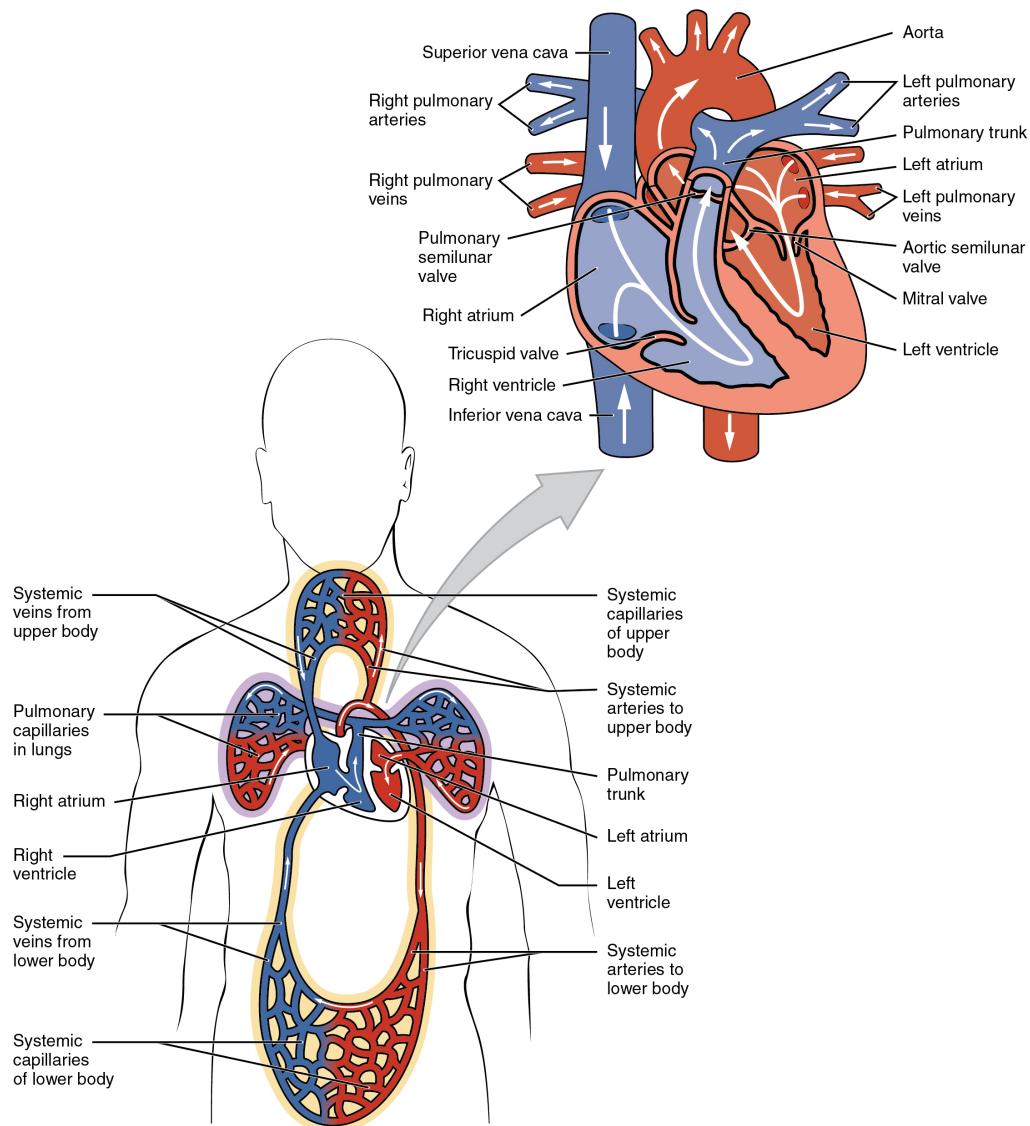
## Chambers and Circulation through the Heart

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 **pulmonary circuit** transports blood to and from the lungs, where it picks up oxygen and delivers carbon dioxide for exhalation. The **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 **pulmonary trunk**, which leads toward the lungs and bifurcates into the left and right **pulmonary arteries**. These vessels in turn branch many times before reaching the **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 **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 **superior vena cava** and the **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 19.4](#)).



**FIGURE 19.4** Dual System of the Human Blood Circulation 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.

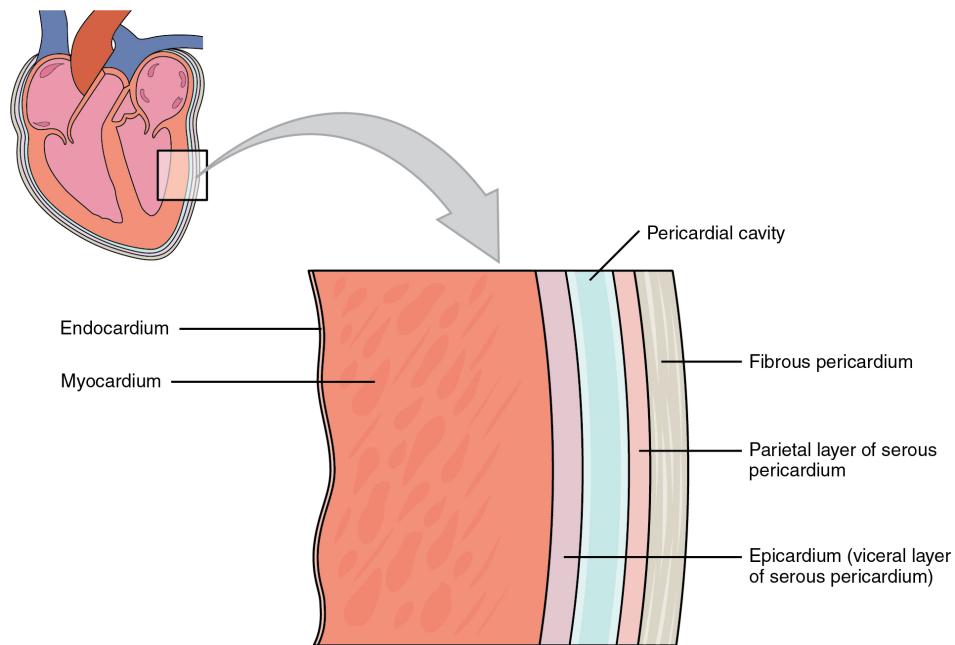
## Membranes, Surface Features, and Layers

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. [Figure 19.5](#) illustrates the pericardial membrane and the layers of the heart.



**FIGURE 19.5 Pericardial Membranes and Layers of the Heart Wall** The pericardial membrane that surrounds the heart consists of three layers and the pericardial cavity. The heart wall also consists of three layers. The pericardial membrane and the heart wall share the epicardium.

### Disorders of the...

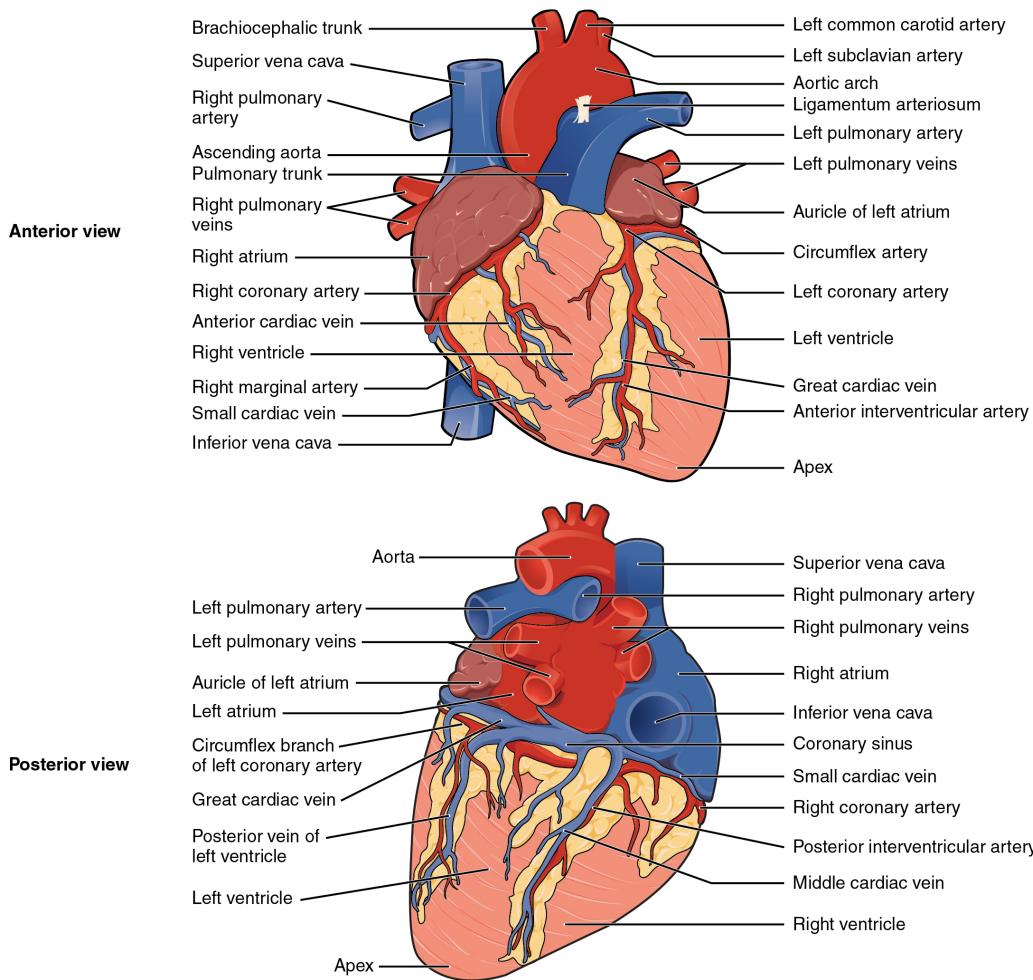
#### Heart: Cardiac Tamponade

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.

### 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 19.6](#)). 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 19.6](#) illustrates anterior and posterior views of the surface of the heart.

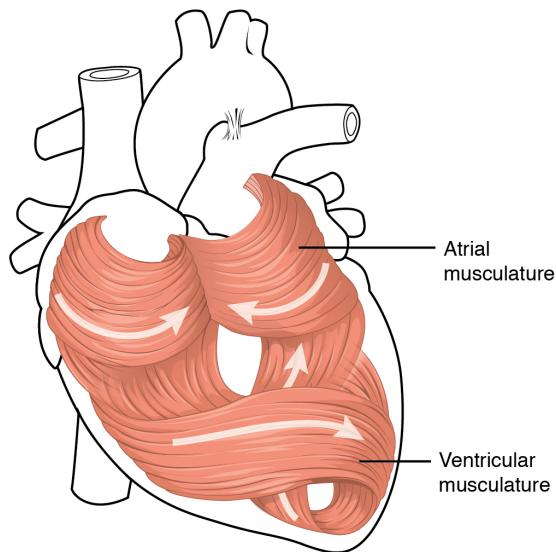


**FIGURE 19.6 External Anatomy of the Heart** Inside the pericardium, the surface features of the heart are visible.

### Layers

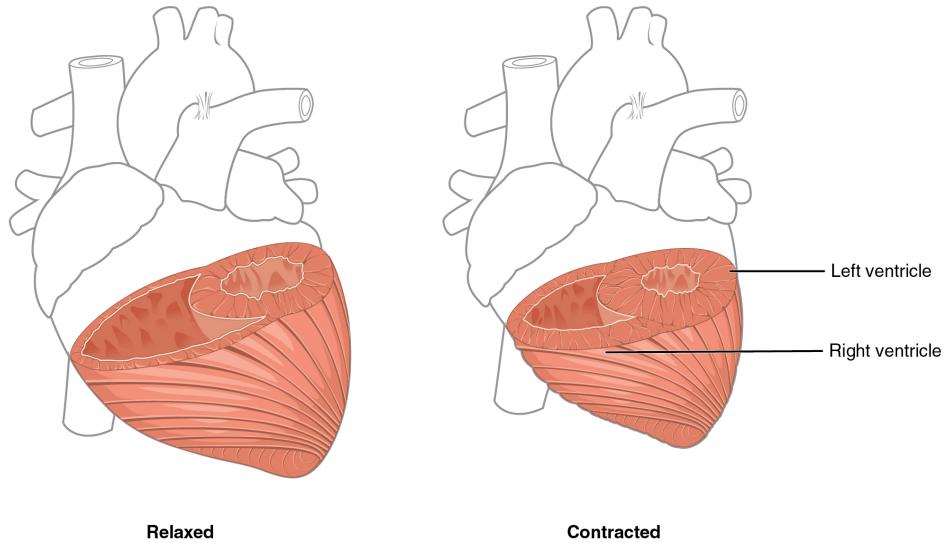
The wall of the heart is composed of three layers of unequal thickness. From superficial to deep, these are the epicardium, the myocardium, and the endocardium (see [Figure 19.5](#)). The outermost layer of the wall of the heart is also the innermost layer of the pericardium, the epicardium, or the visceral 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 19.7](#) illustrates the arrangement of muscle cells.



**FIGURE 19.7 Heart Musculature** The swirling pattern of cardiac muscle tissue contributes significantly to the heart's ability to pump blood effectively.

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. [Figure 19.8](#) illustrates the differences in muscular thickness needed for each of the ventricles.



**FIGURE 19.8 Differences in Ventricular Muscle Thickness** The myocardium in the left ventricle is significantly thicker than that of the right ventricle. Both ventricles pump the same amount of blood, but the left ventricle must generate a much greater pressure to overcome greater resistance in the systemic circuit. The ventricles are shown in both relaxed and contracting states. Note the differences in the relative size of the lumens, the region inside each ventricle where the blood is contained.

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 (see [Figure 19.5](#)).

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

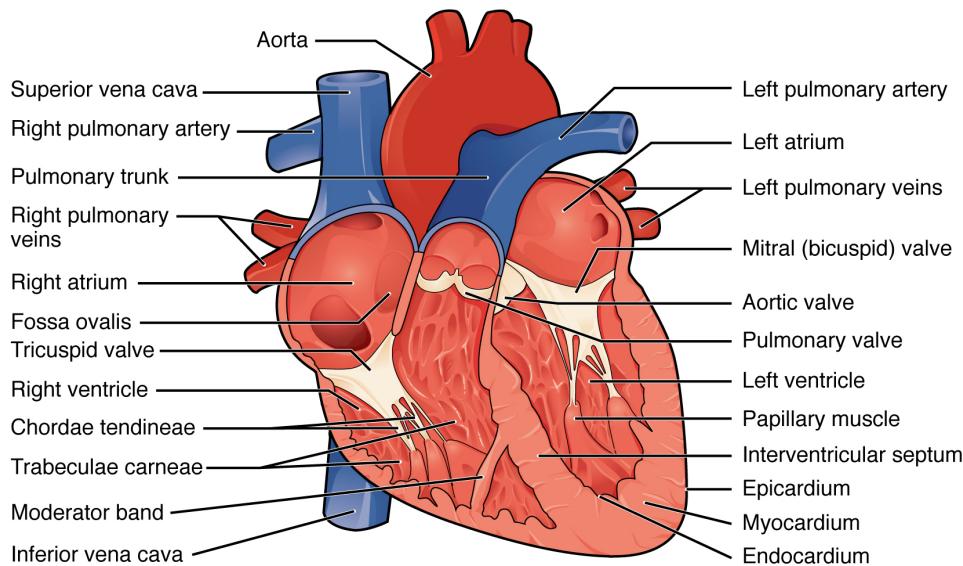
Recall that the heart's contraction cycle follows a dual pattern of circulation—the pulmonary and systemic circuits—because of the pairs of chambers that pump blood into the circulation. In order to develop a more precise understanding of cardiac function, it is first necessary to explore the internal 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 [Figure 19.9](#). In this figure, the atrioventricular septum has been removed to better show the bicuspid 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.

**Anterior view**

**FIGURE 19.9 Internal Structures of the Heart** This anterior view of the heart shows the four chambers, the major vessels and their early branches, as well as the valves. The presence of the pulmonary trunk and aorta covers the interatrial septum, and the atrioventricular septum is cut away to show the atrioventricular valves.

### 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.

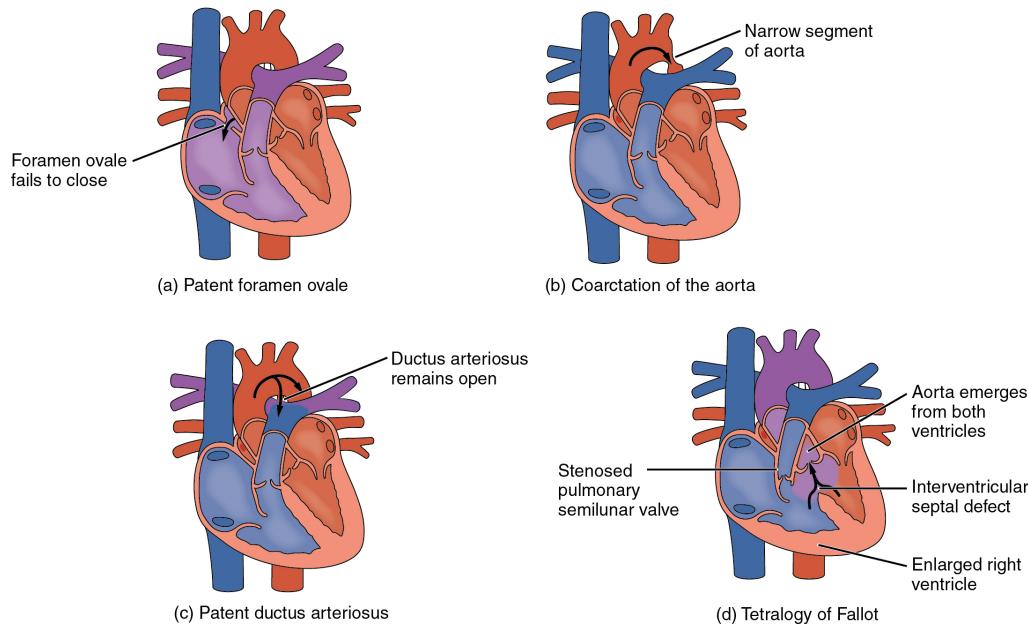
Coarctation of the aorta is a congenital abnormal narrowing of the aorta that is normally located at the insertion of the ligamentum arteriosum, the remnant of the fetal shunt called the ductus arteriosus. If severe, this condition drastically restricts blood flow through the primary systemic artery, 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 19.10](#).



**FIGURE 19.10 Congenital Heart Defects** (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 19.9](#).

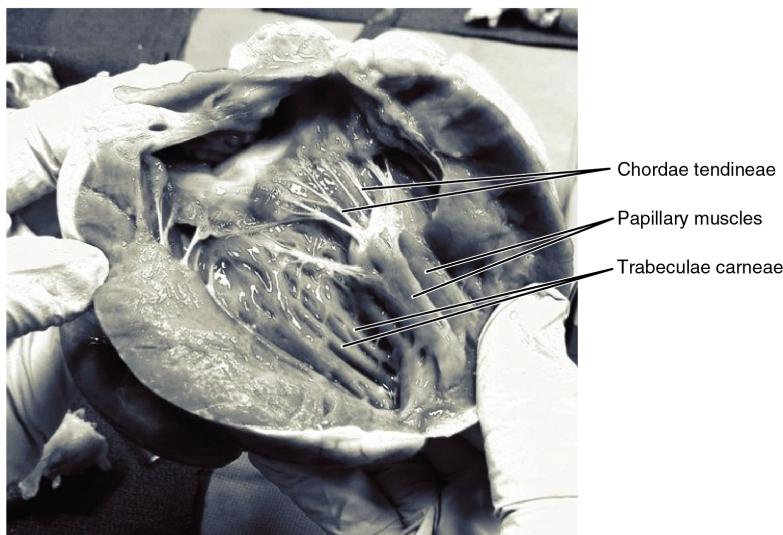
While the bulk of the internal surface of the right atrium is smooth, the depression of the fossa ovalis is medial, and the anterior surface demonstrates prominent ridges of muscle called the **pectinate muscles**. The right auricle also has pectinate muscles. The left atrium does not have pectinate 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. [Figure 19.11](#) shows papillary muscles and chordae tendineae attached to the tricuspid valve.



**FIGURE 19.11 Chordae Tendineae and Papillary Muscles** 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)

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** (see [Figure 19.9](#)) 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.

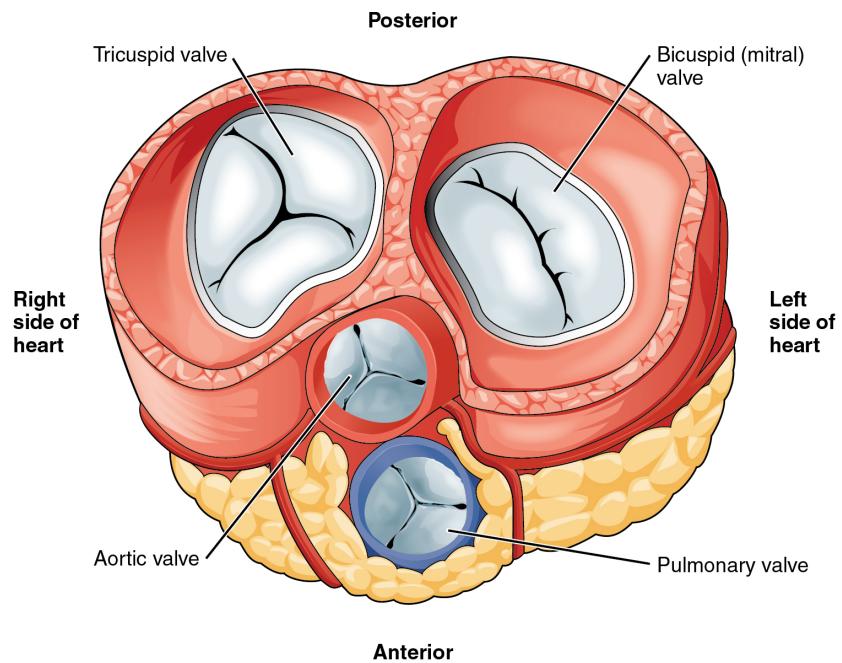
### Left Ventricle

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 (see [Figure 19.8](#)). 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 19.12](#)). 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.



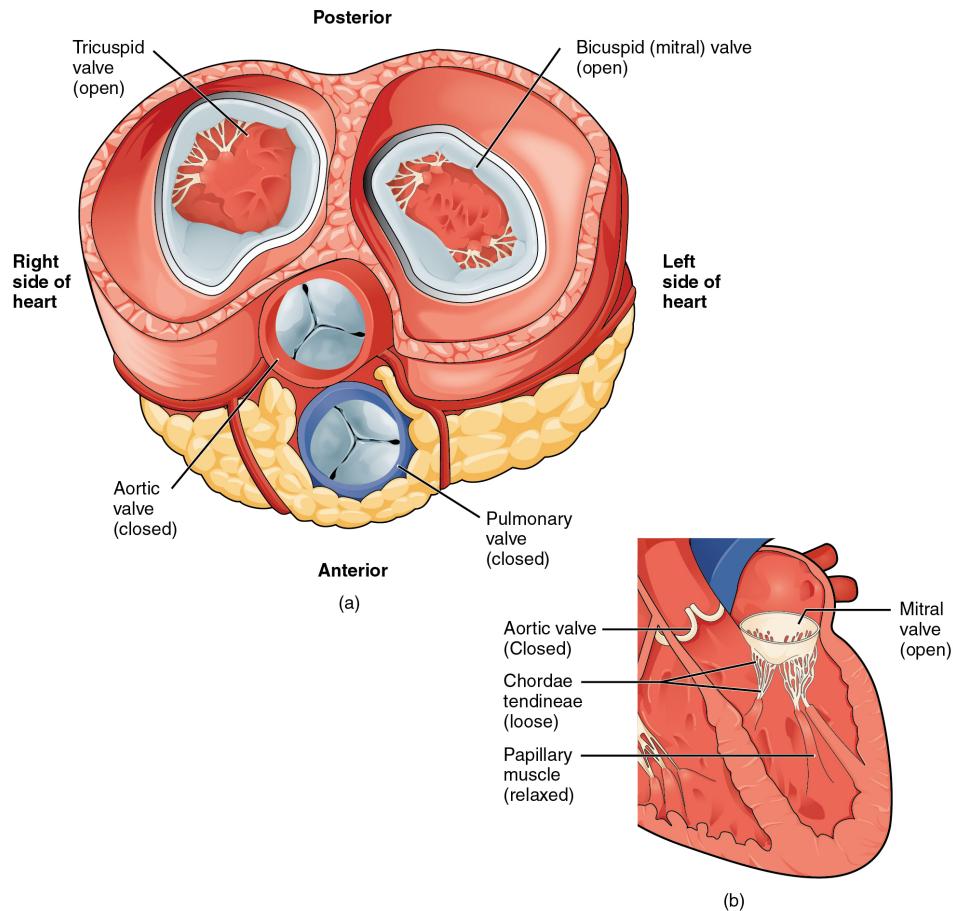
**FIGURE 19.12 Heart Valves** With the atria and major vessels removed, all four valves are clearly visible, although it is difficult to distinguish the three separate cusps of the tricuspid valve.

Emerging from the right ventricle at the base of the pulmonary trunk is the pulmonary semilunar valve, or 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.

Located at the opening between the left atrium and left ventricle is the **mitral valve**, also called the **bicuspid valve** or the **left atrioventricular valve**. Structurally, this valve consists of two cusps, 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.

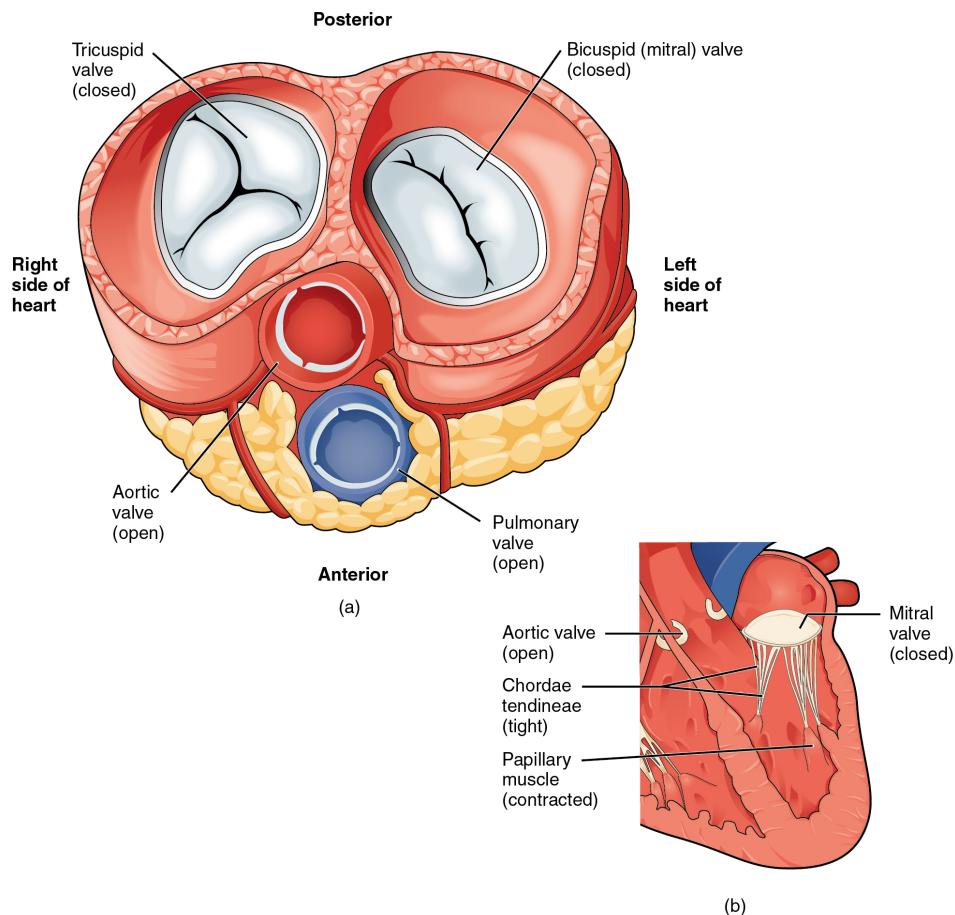
In [Figure 19.13a](#), the two atrioventricular valves are open and the two semilunar valves are closed. This occurs when both atria and ventricles are relaxed and when the atria contract to pump blood into the ventricles. [Figure 19.13b](#) shows a frontal view. Although only the left side of the heart is illustrated, the process is virtually identical on the right.



**FIGURE 19.13** Blood Flow from the Left Atrium to the Left Ventricle (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.

[Figure 19.14a](#) 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 [Figure 19.14b](#).



**FIGURE 19.14** Blood Flow from the Left Ventricle into the Great Vessels (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 (see [Figure 19.13b](#)). However, as the myocardium of the ventricle contracts, so do the papillary muscles. This creates tension on the chordae tendineae (see [Figure 19.14b](#)), 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.

### INTERACTIVE LINK

Visit this [site](http://openstax.org/l/heartvalve) (<http://openstax.org/l/heartvalve>) to observe 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.

### INTERACTIVE LINK

Visit this [site](http://openstax.org/l/heartsounds) (<http://openstax.org/l/heartsounds>) for a free download, including excellent animations and audio of heart sounds.

### 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.

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### INTERACTIVE LINK

Visit this [site](http://openstax.org/l/cardiohist) (<http://openstax.org/l/cardiohist>) to learn more about cardiologists.

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## CAREER CONNECTION

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### 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).

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### INTERACTIVE LINK

Visit this [site](http://openstax.org/l/cardiotech) (<http://openstax.org/l/cardiotech>) for more information on cardiovascular technologists/technicians.

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## 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.

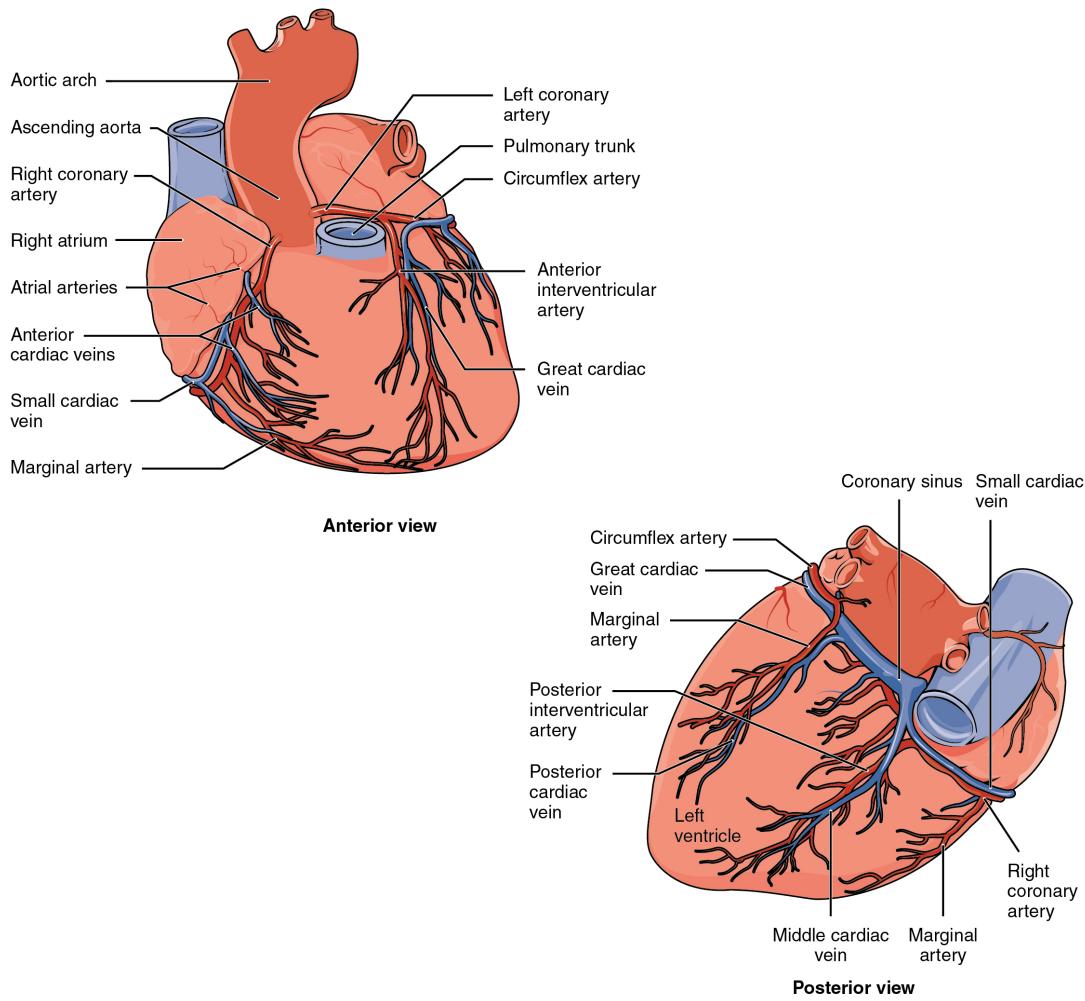
### Coronary Arteries

**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 19.15](#) presents views of the coronary circulation from both the anterior and posterior views.



**FIGURE 19.15 Coronary Circulation** The anterior view of the heart shows the prominent coronary surface vessels. The posterior view of the heart shows the prominent coronary surface vessels.

#### 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 (palpitations), 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

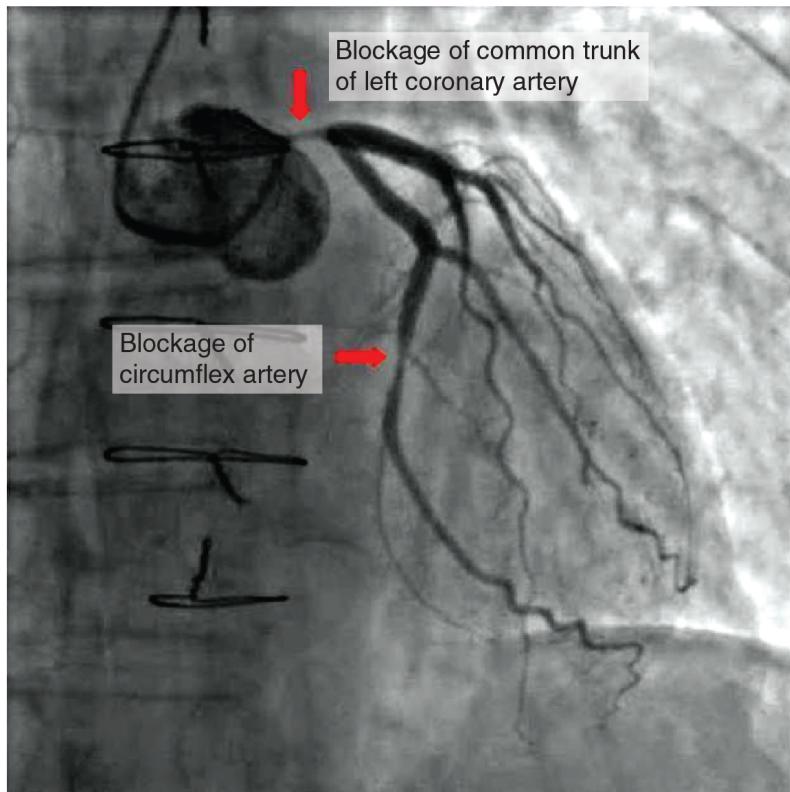
**Coronary veins** drain the heart and generally parallel the large surface arteries (see [Figure 19.15](#)). The **great cardiac vein** can be seen initially on the surface of the heart following the interventricular sulcus, but it eventually flows along the coronary sulcus into the coronary sinus on 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.

## Disorders of the...

### 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. [Figure 19.16](#) 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.



**FIGURE 19.16 Atherosclerotic Coronary Arteries** In this coronary angiogram (X-ray), the dye makes visible two occluded coronary arteries. Such blockages can lead to decreased blood flow (ischemia) and insufficient oxygen (hypoxia) delivered to the cardiac tissues. If uncorrected, this can lead to cardiac muscle death (myocardial infarction).

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.

## 19.2 Cardiac Muscle and Electrical Activity

### LEARNING OBJECTIVES

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

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

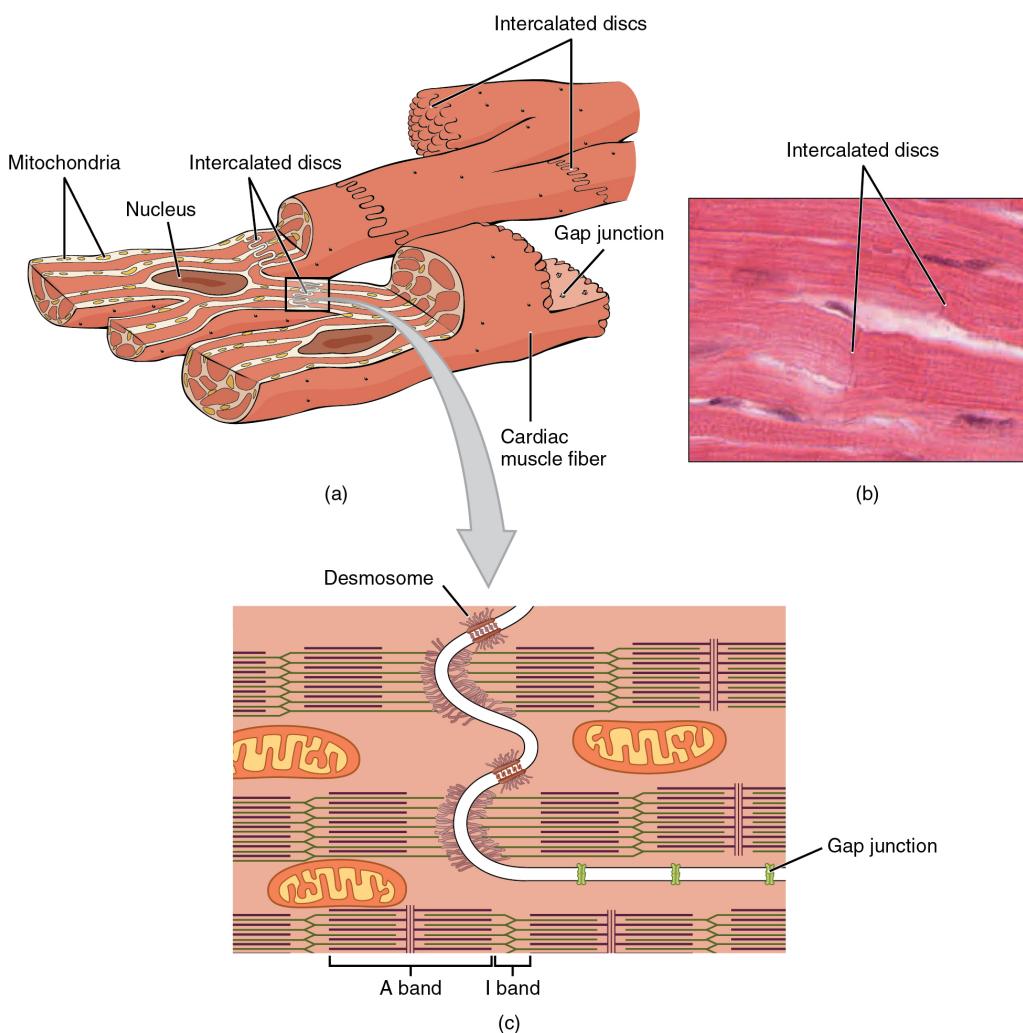
Recall that cardiac muscle shares a few characteristics with both skeletal muscle and smooth muscle, but it has some unique properties of its own. Not the least of these exceptional properties is its ability to initiate an electrical potential at a fixed rate that spreads rapidly from cell to cell to trigger the contractile mechanism. This property is known as **autorhythmicity**. Neither smooth nor skeletal muscle can do this. Even though cardiac muscle has autorhythmicity, heart rate is modulated by the endocrine and nervous systems.

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

### Structure of Cardiac Muscle

Compared to the giant cylinders of skeletal muscle, cardiac muscle cells, or cardiomyocytes, are considerably shorter with much smaller diameters. Cardiac muscle also demonstrates striations, the alternating pattern of dark A bands and light I bands attributed to the precise arrangement of the myofilaments and fibrils that are organized in sarcomeres along the length of the cell ([Figure 19.17a](#)). These contractile elements are virtually identical to skeletal muscle. T (transverse) tubules penetrate from the surface plasma membrane, the sarcolemma, to the interior of the cell, allowing the electrical impulse to reach the interior. The T tubules are only found at the Z discs, whereas in skeletal muscle, they are found at the junction of the A and I bands. Therefore, there are one-half as many T tubules in cardiac muscle as in skeletal muscle. In addition, the sarcoplasmic reticulum stores few calcium ions, so most of the calcium ions must come from outside the cells. The result is a slower onset of contraction. Mitochondria are plentiful, providing energy for the contractions of the heart. Typically, cardiomyocytes have a single, central nucleus, but two or more nuclei may be found in some cells.

Cardiac muscle cells branch freely. A junction between two adjoining cells is marked by a critical structure called an **intercalated disc**, which helps support the synchronized contraction of the muscle ([Figure 19.17b](#)). The sarcolemmas from adjacent cells bind together at the intercalated discs. They consist of desmosomes, specialized linking proteoglycans, tight junctions, and large numbers of gap junctions that allow the passage of ions between the cells and help to synchronize the contraction ([Figure 19.17c](#)). Intercellular connective tissue also helps to bind the cells together. The importance of strongly binding these cells together is necessitated by the forces exerted by contraction.



**FIGURE 19.17 Cardiac Muscle** (a) Cardiac muscle cells have myofibrils composed of myofilaments arranged in sarcomeres, T tubules to transmit the impulse from the sarcolemma to the interior of the cell, numerous mitochondria for energy, and intercalated discs that are found at the junction of different cardiac muscle cells. (b) A photomicrograph of cardiac muscle cells shows the nuclei and intercalated discs. (c) An intercalated disc connects cardiac muscle cells and consists of desmosomes and gap junctions. LM  $\times 1600$ . (Micrograph provided by the Regents of the University of Michigan Medical School © 2012)

Cardiac muscle undergoes aerobic respiration patterns, primarily metabolizing lipids and carbohydrates. Myoglobin, lipids, and glycogen are all stored within the cytoplasm. Cardiac muscle cells undergo twitch-type contractions with long refractory periods followed by brief relaxation periods. The relaxation is essential so the heart can fill with blood for the next cycle. The refractory period is very long to prevent the possibility of tetany, a condition in which muscle remains involuntarily contracted. In the heart, tetany is not compatible with life, since it would prevent the heart from pumping blood.

### Everyday Connection

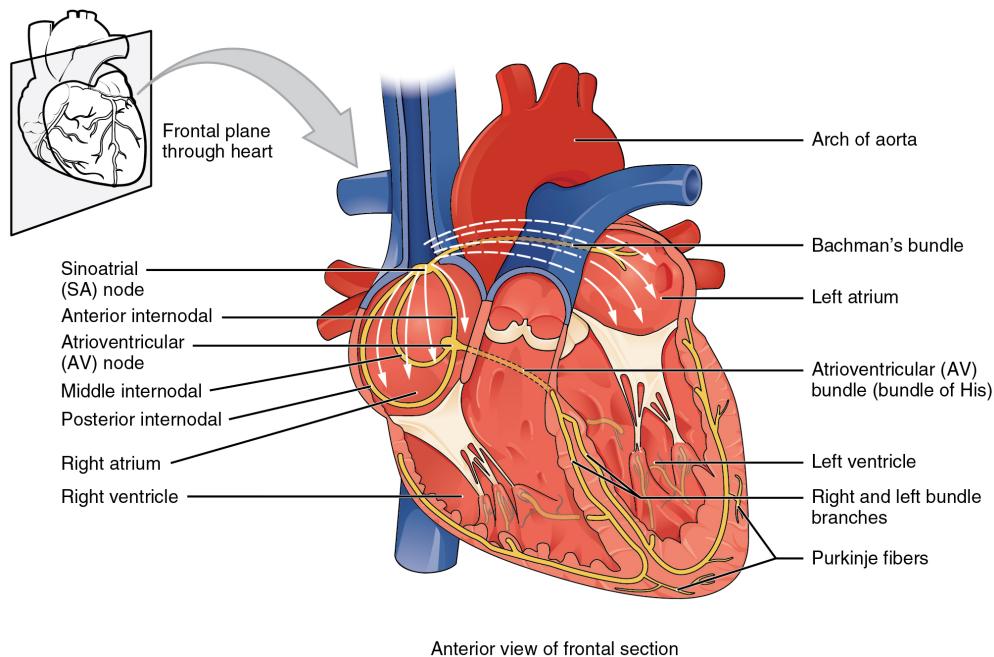
#### Repair and Replacement

Damaged cardiac muscle cells have extremely limited abilities to repair themselves or to replace dead cells via mitosis. Recent evidence indicates that at least some stem cells remain within the heart that continue to divide and at least potentially replace these dead cells. However, newly formed or repaired cells are rarely as functional as the original cells, and cardiac function is reduced. In the event of a heart attack or MI, dead cells are often replaced by patches of scar tissue. Autopsies performed on individuals who had successfully received heart transplants show some proliferation of original cells. If researchers can unlock the mechanism that generates new cells and restore full mitotic capabilities to heart muscle, the prognosis for heart attack survivors

will be greatly enhanced. To date, myocardial cells produced within the patient (*in situ*) by cardiac stem cells seem to be nonfunctional, although those grown in Petri dishes (*in vitro*) do beat. Perhaps soon this mystery will be solved, and new advances in treatment will be commonplace.

## Conduction System of the Heart

If embryonic heart cells are separated into a Petri dish and kept alive, each is capable of generating its own electrical impulse followed by contraction. When two independently beating embryonic cardiac muscle cells are placed together, the cell with the higher inherent rate sets the pace, and the impulse spreads from the faster to the slower cell to trigger a contraction. As more cells are joined together, the fastest cell continues to assume control of the rate. A fully developed adult heart maintains the capability of generating its own electrical impulse, triggered by the fastest cells, as part of the cardiac conduction system. The components of the cardiac conduction system include the sinoatrial node, the atrioventricular node, the atrioventricular bundle, the atrioventricular bundle branches, and the Purkinje cells (Figure 19.18).



Anterior view of frontal section

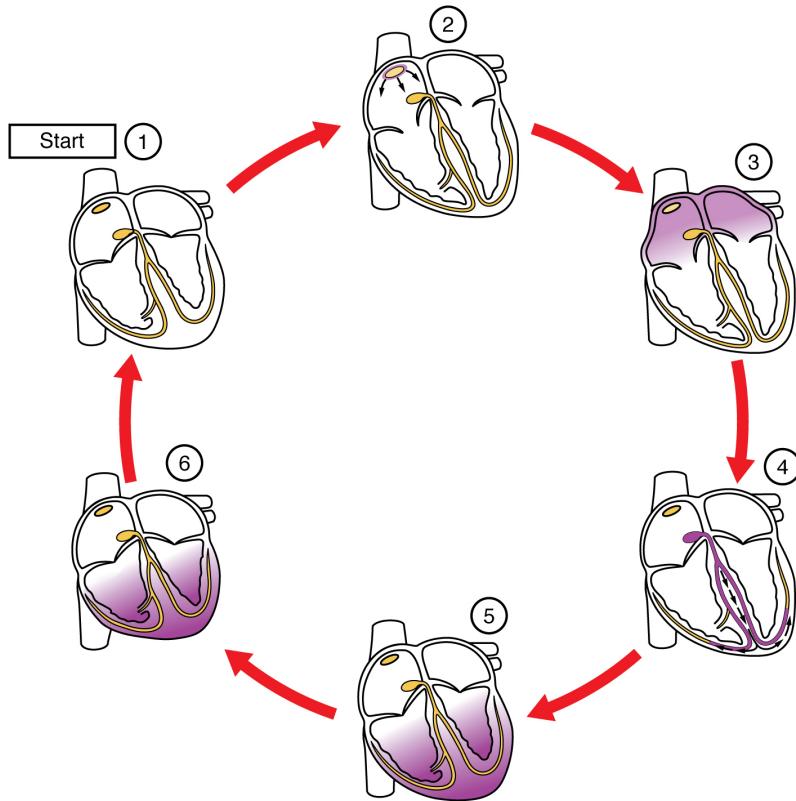
**FIGURE 19.18 Conduction System of the Heart** Specialized conducting components of the heart include the sinoatrial node, the internodal pathways, the atrioventricular node, the atrioventricular bundle, the right and left bundle branches, and the Purkinje fibers.

### Sinoatrial (SA) Node

Normal cardiac rhythm is established by the **sinoatrial (SA) node**, a specialized clump of myocardial conducting cells located in the superior and posterior walls of the right atrium in close proximity to the orifice of the superior vena cava. The SA node has the highest inherent rate of depolarization and is known as the **pacemaker** of the heart. It initiates the **sinus rhythm**, or normal electrical pattern followed by contraction of the heart.

This impulse spreads from its initiation in the SA node throughout the atria through specialized **internodal pathways**, to the atrial myocardial contractile cells and the atrioventricular node. The internodal pathways consist of three bands (anterior, middle, and posterior) that lead directly from the SA node to the next node in the conduction system, the atrioventricular node (see Figure 19.18). The impulse takes approximately 50 ms (milliseconds) to travel between these two nodes. The relative importance of this pathway has been debated since the impulse would reach the atrioventricular node simply following the cell-by-cell pathway through the contractile cells of the myocardium in the atria. In addition, there is a specialized pathway called **Bachmann's bundle** or the **interatrial band** that conducts the impulse directly from the right atrium to the left atrium. Regardless of the pathway, as the impulse reaches the atrioventricular septum, the connective tissue of the cardiac skeleton prevents the impulse from spreading into the myocardial cells in the ventricles except at the atrioventricular node. Figure 19.19 illustrates the initiation of the impulse in the SA node that then spreads the impulse throughout the atria to

the atrioventricular node.



**FIGURE 19.19 Cardiac Conduction** (1) The sinoatrial (SA) node and the remainder of the conduction system are at rest. (2) The SA node initiates the action potential, which sweeps across the atria. (3) After reaching the atrioventricular node, there is a delay of approximately 100 ms that allows the atria to complete pumping blood before the impulse is transmitted to the atrioventricular bundle. (4) Following the delay, the impulse travels through the atrioventricular bundle and bundle branches to the Purkinje fibers, and also reaches the right papillary muscle via the moderator band. (5) The impulse spreads to the contractile fibers of the ventricle. (6) Ventricular contraction begins.

The electrical event, the wave of depolarization, is the trigger for muscular contraction. The wave of depolarization begins in the right atrium, and the impulse spreads across the superior portions of both atria and then down through the contractile cells. The contractile cells then begin contraction from the superior to the inferior portions of the atria, efficiently pumping blood into the ventricles.

#### Atrioventricular (AV) Node

The **atrioventricular (AV) node** is a second clump of specialized myocardial conductive cells, located in the inferior portion of the right atrium within the atrioventricular septum. The septum prevents the impulse from spreading directly to the ventricles without passing through the AV node. There is a critical pause before the AV node depolarizes and transmits the impulse to the atrioventricular bundle (see [Figure 19.19](#), step 3). This delay in transmission is partially attributable to the small diameter of the cells of the node, which slow the impulse. Also, conduction between nodal cells is less efficient than between conducting cells. These factors mean that it takes the impulse approximately 100 ms to pass through the node. This pause is critical to heart function, as it allows the atrial cardiomyocytes to complete their contraction that pumps blood into the ventricles before the impulse is transmitted to the cells of the ventricle itself. With extreme stimulation by the SA node, the AV node can transmit impulses maximally at 220 per minute. This establishes the typical maximum heart rate in a healthy young individual. Damaged hearts or those stimulated by drugs can contract at higher rates, but at these rates, the heart can no longer effectively pump blood.

#### Atrioventricular Bundle (Bundle of His), Bundle Branches, and Purkinje Fibers

Arising from the AV node, the **atrioventricular bundle**, or **bundle of His**, proceeds through the interventricular septum before dividing into two **atrioventricular bundle branches**, commonly called the left and right bundle branches. The left bundle branch has two fascicles. The left bundle branch supplies the left ventricle, and the right bundle branch the right ventricle. Since the left ventricle is much larger than the right, the left bundle branch is also