

# 1

## Nervous Tissue

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The nervous system has two categories of cells, neurons (Greek *neuron*, nerve) and neuroglia (Greek *glia*, glue). Their names reflect the fact that neurons give rise to nerves, while neuroglia are thought of as cells simply holding neurons together. Neurons and neuroglia are far more complex in their shape than cells in any other tissue. Their morphological heterogeneity reflects the functional complexity of the nervous system. Neurons and neuroglia play different roles in the nervous tissue. Neurons are specialized in information processing. Specialized contact areas called synapses mediate signals from one neuron to others. Synapses are the basis of complex neuronal networks designed for information processing. Neurons stop dividing within a few months after birth. Therefore, if nerve damage involves cell bodies in the adult animal, resulting neuronal death will permanently change the structure and functions of the affected areas. Unlike neurons, neuroglia continue to divide. This glial capacity to divide is essential for their structural and functional support of neurons. Neurons and glial cells require a chemically stable environment. Endothelial cells of the central nervous system and the choroid plexus help maintain such an environment by regulating molecules secreted into the interstitial fluid and cerebrospinal fluid (CSF).

All nervous tissue other than the cerebrum, brainstem, cerebellum, and spinal cord is referred to as the **peripheral nervous system (PNS)**. The PNS comprises the nerves, ganglia (spinal, cranial, sympathetic trunk, collateral, terminal), and sensory receptors. The PNS conveys (i) sensory signals about the external and internal environment of the body to the CNS and (ii) motor signals from the CNS to the peripheral effectors (skeletal muscle, cardiac muscle, smooth muscle, secretory glands). Certain neural components of the CNS and PNS regulate the visceral organs, smooth muscles (e.g., vascular, pupillary dilator, pupillary sphincter, ciliary, orbital, arrector pili), and glands (salivary, lacrimal, nasal, adrenal). These neural components of the CNS and PNS are collectively referred to as the **autonomic nervous system (ANS)**. The ANS is, in general, not under voluntary control, but rather its action is controlled by the hypothalamus. The ANS consists of many specialized neural components (e.g., nuclei, ganglia, nerves, tracts and visceral plexus). For example, the increased heart rate in the “fight or flight” response involves the hypothalamus (i.e., CNS), intermediolateral nucleus in the spinal cord (i.e., CNS), ganglia (i.e., PNS) and peripheral nerves (i.e., PNS).

### Division of the nervous system

- 1 Differentiate between the central nervous system and the peripheral nervous system.
- 2 What is the relationship between the autonomic and the central nervous systems?

The nervous system can be classified into three systems: the central nervous system, peripheral nervous system and autonomic nervous system. The **central nervous system (CNS)** is composed of the cerebrum, cerebellum, brainstem, and spinal cord. It is the central processing unit of the entire nervous

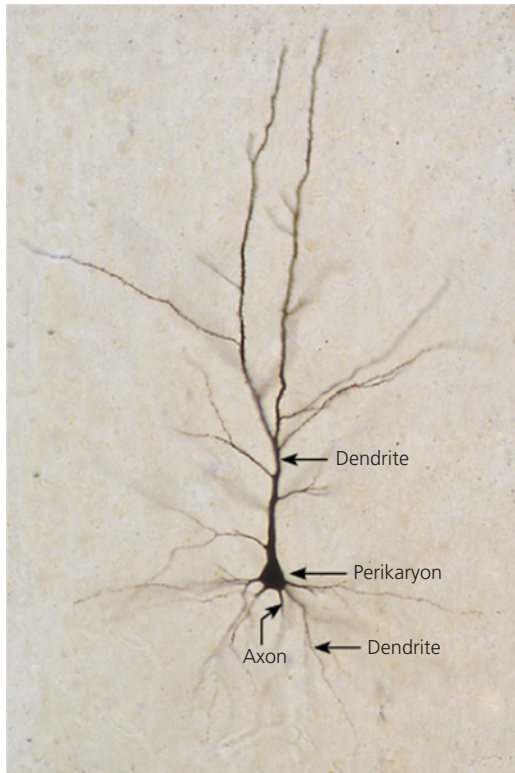
### Cells of the nervous system

- 1 What are three different types of neurons?
- 2 What are the functions of an axon and a dendrite?
- 3 What is the axon hillock? What is its functional significance?
- 4 What are the structural and functional differences between myelinated and nonmyelinated axons?
- 5 Name the neuroglia of the CNS and PNS, and explain their functions.
- 6 How do Schwann cells differ from oligodendrocytes?
- 7 What are the bases of classifying peripheral nerve fibers?

Neurons and neuroglia are the two categories of cells of the nervous system. **Neurons** share certain universal cellular features with all other cells in the body; however, neurons have certain unique features that separate them from other cells. For example, they have distinctive cell shapes with a membrane capable of generating electrical impulses. They transfer impulses from one neuron to the next via synapses (Greek *synapsis*, a connection), the specialized contact areas between two neurons. Although transmission of impulses is a basic biological function performed by all neurons, their electrical property alone does not explain the diverse roles they play in a complex neural network. **Neuroglia** are the most abundant cells in nervous tissue (over 90%), filling essentially all the space in the nervous system not occupied by neurons and blood vessels. They provide structural, metabolic, and protective support for neurons.

### Neurons

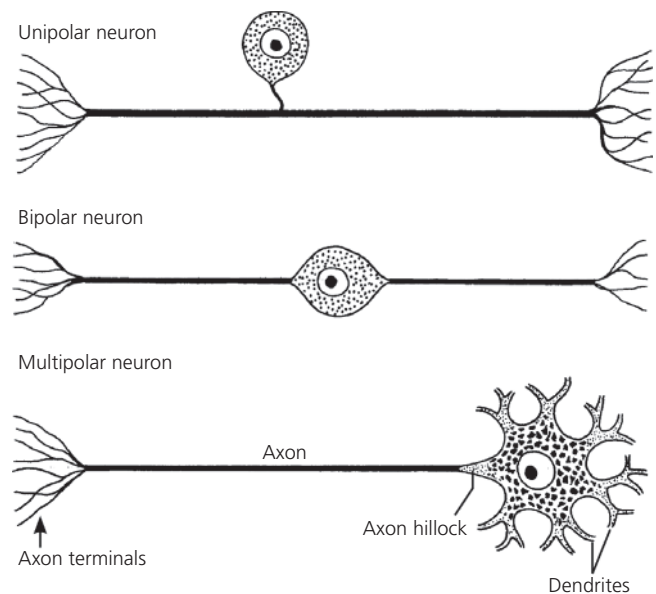
The most obvious difference between neurons and other cells in the body lies in their great variety of shapes and sizes. Neurons have highly irregular shapes with one or more cellular processes extending from the cell body (Figure 1.1). The **neuronal cell body** (also referred to as the **soma** or **perikaryon**) contains the same organelles found in other cells. However, the rough endoplasmic reticulum and polysomes (collectively referred to



**Figure 1.1** A cortical multipolar neuron stained with the Golgi silver impregnation method showing the perikaryon, axon, and dendrites. Only one axon emerges from the perikaryon. All other neuronal processes are dendrites.

as **Nissl substance**) are especially abundant in perikarya. Each neuron has a single axon. The area of the cell body where an axon originates is the **axon hillock**. The axon hillock is also referred to as the trigger zone, as action potentials are generated here. Just distal to the axon hillock is the **initial segment** of the axon.

Axons frequently branch at a distance from the cell body, forming synapses with other neurons, muscle cells, or glands. The remaining neuronal processes are **dendrites** (Greek *dentron*, tree) that resemble trees (Figure 1.1). Dendrites and perikarya are the primary receptive sites of impulses from other neurons. The number of dendrites varies depending on the type of neuron (Figure 1.2). Action potentials are generated at the axon hillock. An action potential travels along the axon at a speed that varies from 0.5 to 120 m/s. Larger axons, over 1  $\mu\text{m}$  in diameter, are myelinated in both the CNS and PNS, while axons less than 1  $\mu\text{m}$  in diameter are not myelinated. Myelinated axons conduct impulses much faster than nonmyelinated axons. There is a constant relationship between axon diameter, internodal length (i.e., length of each myelin sheath), and conduction velocity. Larger axons have longer internodes and faster conduction velocities. Neurons are contiguous not continuous and they communicate with each other via synapses. If a neuron is linked to more than one recipient neuron, its axon branches to make synaptic connections with all the recipient neurons. Neurons, like muscle cells, do not divide once they reach maturity. Therefore, any physical injury that leads to neuronal death will permanently change the structure and functions of the affected areas.



**Figure 1.2** The classification of neurons is based on the number of cell processes emerging from the cell body. Cell bodies of unipolar neurons are present in the spinal and cranial ganglia. Cell bodies of bipolar neurons are present in the retina of the eye, spiral ganglia of the auditory nerve, vestibular ganglia of the vestibular nerve, and olfactory epithelium. The majority of neurons are multipolar neurons.

The color of fresh nervous tissue reflects neuronal cell bodies and axons. Areas with a high population of perikarya (e.g., cerebral cortex) appear gray and are referred to as the **gray matter**. In contrast, areas mainly made of myelinated axons appear white because of the presence of lipid in myelin. The name **white matter** is used to indicate such areas.

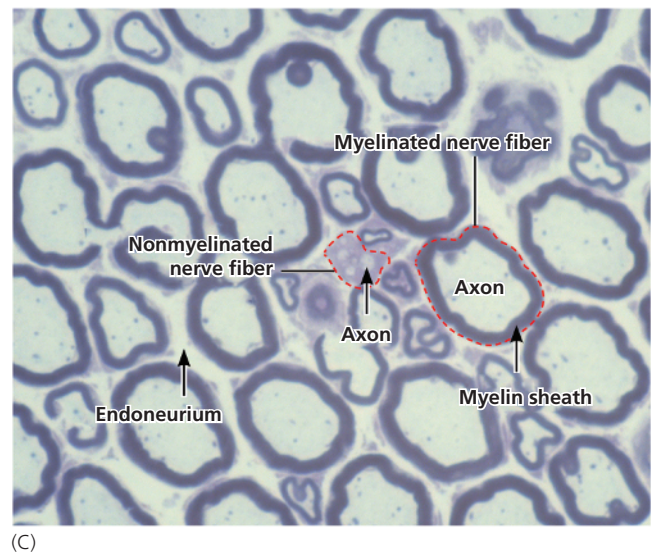
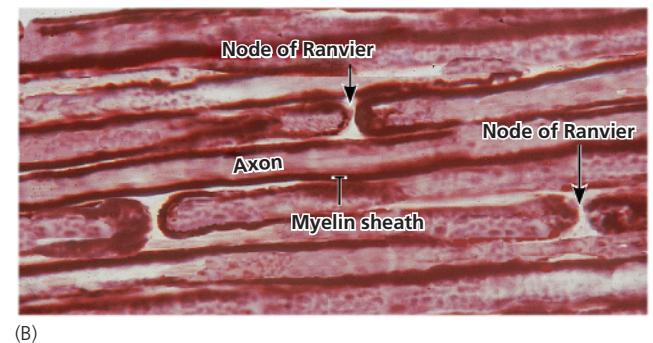
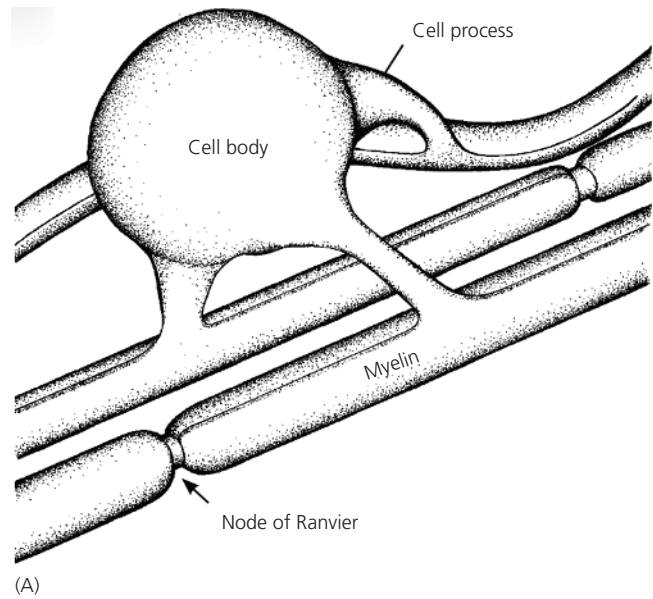
### Classification of neurons

Neurons are classified into three types (unipolar, bipolar, and multipolar) based on the number of cellular processes extending from the cell body (Figure 1.2). **Unipolar neurons** have a single stem process that bifurcates to form two processes, the peripheral and central. Unipolar neurons innervate peripheral tissues, bringing somatic and visceral sensory information to the CNS. Thus they are also referred to as primary sensory neurons. **Bipolar neurons** have two processes. Bipolar neurons are located in the retina of the eye (see Figure 7.4), spiral ganglion of the cochlea (see Figure 6.2B), vestibular ganglion of the vestibular organ (see Figure 9.1), and olfactory epithelium (see Figure 5.2). Bipolar neurons are sensory neurons. Their peripheral processes innervate sensory receptors, bringing sensory signals to the CNS. An exception to this rule is the olfactory cells. A terminal branch of the olfactory cell forms a dendritic bulb and its cilia act as receptors detecting the chemical environment in nasal air. **Multipolar neurons** are the most prevalent type. As the name “multipolar” suggests, each neuron has numerous cell processes (one axon and many dendrites). The length and arrangement of neuronal processes vary considerably.

### Neuroglia

Neuroglia are generally small in size and outnumber neurons by as much as 10 : 1 to 50 : 1. Their small size is such that only their nuclei are clearly seen in routine histological preparations. The nuclei range in diameter from 3 to 10  $\mu\text{m}$ , which is about the size of the smallest neurons. Unlike neurons, neuroglia have the capacity to divide. Schwann cells are the only neuroglia of the PNS. Neuroglia of the CNS are oligodendrocytes, ependymal cells, microglia, and astrocytes.

**Schwann cells** (also referred to as neurolemmocytes) support axons of the PNS, depending on the size of the axon, in two ways. Schwann cells associated with most axons over 1  $\mu\text{m}$  in diameter form myelin sheaths by concentrically wrapping their plasma membrane around the axon (up to 50 or more layers) (Figure 1.3C). Schwann cells are arranged side by side along the axon. Each Schwann cell forms an **internode** of the myelin sheath of various lengths (25–1000  $\mu\text{m}$ ). The larger axons have longer internodes and faster conduction speed. The junction between each internode is the **node of Ranvier** (Figure 1.3B). Schwann cells are also associated with most axons less than 1  $\mu\text{m}$  in diameter. Schwann cells associated with smaller axons do not form a myelin sheath, but they hold many smaller axons in their processes. **Oligodendrocytes** (Greek *oligos*, little; *dendron*, dendrite) are small neuroglia of the CNS. They are present



**Figure 1.3** (A) Oligodendrocytes myelinate most axons about 1  $\mu\text{m}$  and over in diameter. Each oligodendrocyte contributes segments of myelin sheath (i.e., internodes) for many axons. (B) Longitudinal section of a peripheral nerve showing axons and their darkly stained myelin sheath, and nodes of Ranvier. (C) Electron micrograph of nonmyelinated and myelinated axons. Nonmyelinated axons are much smaller in size than myelinated ones. Each axon is surrounded by endoneurium.

in both the white and gray matter. Oligodendrocytes have numerous cell processes that extend to adjacent axons to form myelin sheaths (Figure 1.3A). Generally, oligodendrocytes myelinate most axons over 1  $\mu\text{m}$  in diameter to speed conduction velocity (Tables 1.1 and 1.2).

**Table 1.1** Classification of peripheral nerve fibers by the letter system.

Type	Diameter ( $\mu\text{m}$ )	Conduction velocity (m/s)	Function
A $\alpha$	12–22	70–120	Somatic motor, proprioception
A $\beta$	5–12	30–70	Touch, pressure
A $\gamma$	3–8	15–30	Motor to muscle spindle
A $\delta$	1–5	12–30	Fast pain and temperature
B	1–3	3–15	Visceral motor (preganglionic)
C	0.3–1.5	0.3–1.5	Visceral motor (postganglionic), slow pain and temperature

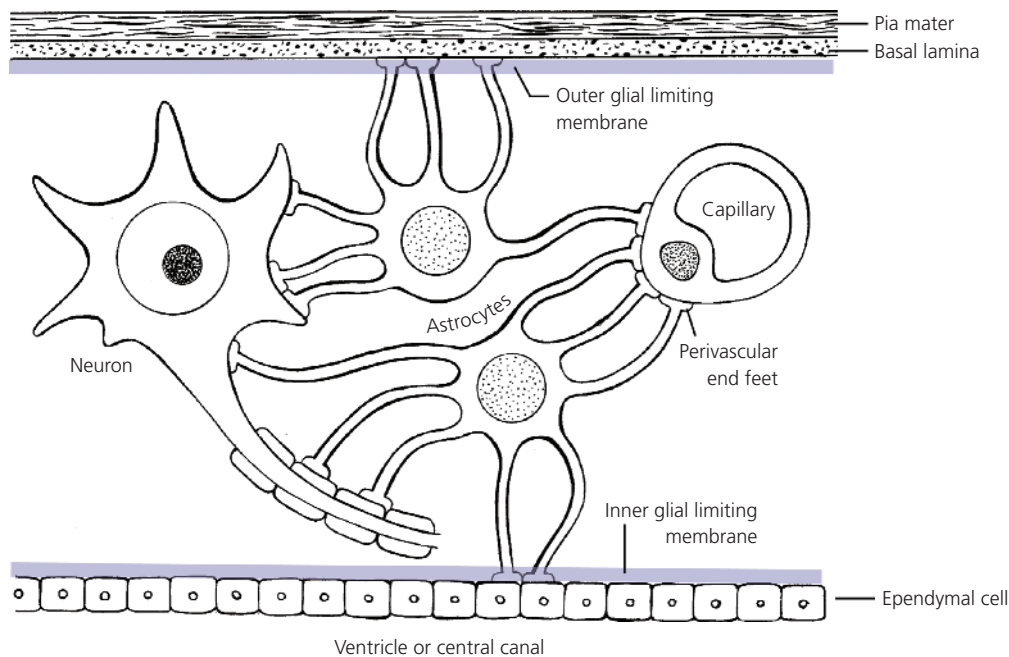
**Table 1.2** Classification of peripheral sensory nerve fibers by the numerical system.

Type	Letter equivalent	Diameter ( $\mu\text{m}$ )	Origin
Ia	A $\alpha$	12–22	Muscle spindle (primary)
Ib	A $\alpha$	10–15	Golgi tendon organ
II	A $\beta$ , A $\gamma$	5–12	Muscle spindle (secondary), touch, pressure
III	A $\delta$	1–5	Fast pain and temperature
IV	C	0.3–1.5	Slow pain and temperature

An axon and myelin sheath (if present) together form a **nerve fiber**. Peripheral nerve fibers vary in diameter, ranging from 0.3 to 22  $\mu\text{m}$ . Nerve fibers are classified according to their fiber diameter, speed of conduction, and functions. The largest nerve fibers are classified as A $\alpha$  and the smallest ones as C (Table 1.1). Since the conduction velocity reflects myelination and the axonal diameter, A $\alpha$  nerve fibers that innervate the skeletal muscle are heavily myelinated and have the fastest conduction velocity. Other type A ( $\beta$ ,  $\gamma$ ,  $\delta$ ) and B nerve fibers are progressively smaller and poorly myelinated. Most nerve fibers classified as C are not myelinated and have a slow conduction velocity. A numerical system (I, II, III, IV) is used to classify sensory nerve fibers (Table 1.2). The largest sensory fibers are classified as Ia and the smallest ones as IV. Type IV sensory fibers are mostly nonmyelinated.

**Microglia** comprise 10–20% of all neuroglia. Microglia are the macrophages of the CNS and act as the first line of defense against tissue injury or infection. Once activated, microglia proliferate and assume a phagocytic role by developing into round, often large cells. They clear debris from the injured area. However, phagocytosis is not the only means of destroying foreign invaders. For example, microglia are also known to release nitric oxide, which prevents viral replication.

**Astrocytes** (Greek *astron*, star) are star-shaped cells with numerous long cell processes (Figure 1.4). However, they appear as cells with pale ovoid nuclei with routine staining. Astrocytes represent approximately 50% of the glial cell population in the CNS. They provide structural and metabolic support for neurons. For example, astrocytes seal the outer and inner surfaces of the CNS by forming the outer and



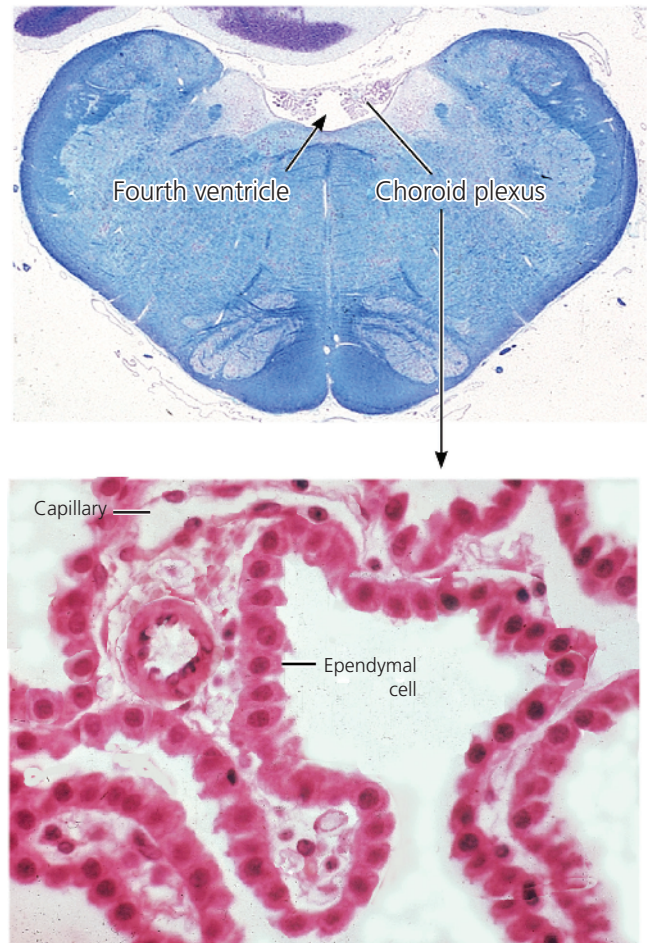
**Figure 1.4** Relationship of astrocytes to other cellular and structural components of the central nervous system. Astrocytic processes surround neurons, individual or groups of synapses, capillaries and internodal areas between myelin sheaths. They also form a plexus beneath the pia mater (outer glial limiting membrane) and ependyma (inner glial limiting membrane).

inner glial limiting membranes, respectively. Astrocytes release **neurotrophic factors** (e.g., nerve growth factor), which are important for neuronal survival. Elongation of axons and dendrites requires not only the physical presence of astrocytes, but also **extracellular adhesion molecules** (e.g., laminin, fibronectin) released from astrocytes. Astrocytic processes cover the greater part of neurons, synaptic sites, internodal areas, and capillaries. Astrocytic covering of synaptic sites and internodal areas may prevent signal interference from nearby synapses and axons.

The astrocytic processes that cover capillaries are the **perivascular end feet**. Experimental studies suggest that such close contact between astrocytes and the capillary endothelium is important for glucose transport, regulation of extracellular environment (pH, ion concentration, osmolarity), glutamate metabolism, and maintenance of the endothelial blood–brain barrier. Astrocytes maintain the optimal extracellular environment for neurons and neuroglia. For example, astrocytes are equipped with ionic channels for potassium ( $K^+$ ), sodium ( $Na^+$ ), chloride ( $Cl^-$ ), bicarbonate ( $HCO_3^-$ ) and calcium ( $Ca^{2+}$ ). Therefore, they are capable of exchanging these ions with neighboring cells, including neurons. Excitation of neurons accompanies a marked flux of  $K^+$  into the extracellular space. However, an increase in  $K^+$  concentration is prevented by astrocytes, which take up  $K^+$  and relocate it to areas with low neuronal activities or release it to the blood and CSF. Astrocytes also prevent the build-up of potentially neurotoxic substances. Glutamate, for example, is a neurotransmitter that excites postsynaptic neurons (see Figure 3.2B). It is also neurotoxic if accumulated beyond a certain concentration. Astrocytes prevent excess accumulation of extracellular glutamate by metabolizing glutamate into glutamine. Glutamine from astrocytes is used by neurons for synthesis of new glutamate, which is repackaged into synaptic vesicles to be used as a neurotransmitter.

Astrocytes participate in the repair process following tissue injury. Under slowly degenerative conditions, astrocytes retain their small size. Thus only special stains can observe their reactive cytoplasm and cell processes. However, typical astrocytic reactions to pathological conditions are cellular swelling and hyperplasia (Greek *hyper*, above; *plasis*, formation; a condition characterized by an increase in the number of cells). Astrocytic swelling is often induced by injuries from hypoxia (a condition where oxygen levels are below normal), trauma, and hypoglycemia (Greek *hypo*, under; *glykys*, sweet; *haima*, blood; the presence of low sugar levels in the blood). Swelling usually reflects changes in extracellular ionic concentrations (e.g., increase in  $K^+$ , decrease in  $Na^+$  and  $Cl^-$ , accumulation of glutamate). Destructive lesions of the CNS, especially those caused by trauma, promote astrocytic hyperplasia. In a cerebral infarct, i.e., an area of necrosis (Greek *nekrosis*, deadness; death of tissue) resulting from insufficient blood supply, astrocytes proliferate along the edge of the necrotic area, often sealing off the lesioned area.

**Ependymal cells** (Greek *ependyma*, upper garment) cover the ventricles and central canal of the CNS (Figure 1.5). They



**Figure 1.5** The choroid plexus in the fourth ventricle of the medulla oblongata. The choroid plexus is composed of vascular connective tissue lined with ependymal cells on the ventricular surface.

**Table 1.3** Normal CSF values.

Color:	clear
Cells:	<5/mm <sup>3</sup>
Protein:	<25 mg/dL
Glucose:	2.7–4.2 mmol/L
Pressure:	<170 mmH <sub>2</sub> O

also line the choroid plexus. The ependymal cells of the ventricles and central canal form a selective barrier between the nervous tissue and **CSF**. Junctional complexes are present between adjacent ependymal cells, enabling them to modify the CSF by secretory or absorptive processes. The choroid plexus secretes CSF (Table 1.3). However, it is not the only source of CSF. CSF is also released from the brain through (i) the ependymal lining of the ventricles and central canal and (ii) the pia–outer glial limiting membrane that covers the external surface of the CNS.

The CSF leaves the ventricular system via a small opening, the lateral aperture of the fourth ventricle, to enter the subarachnoid space. It also enters the central canal of the caudal medulla oblongata and spinal cord. The CSF in the subarachnoid

space is drained into the dorsal sagittal sinus, which also receives numerous tributary veins from the cerebral hemispheres and passes blood to the maxillary, internal jugular and vertebral veins and to the vertebral venous plexuses. The CSF in the subarachnoid space of the meninges not only protects the brain and spinal cord from trauma, but also reduces the effective weight of the brain significantly by providing a buoyancy effect.

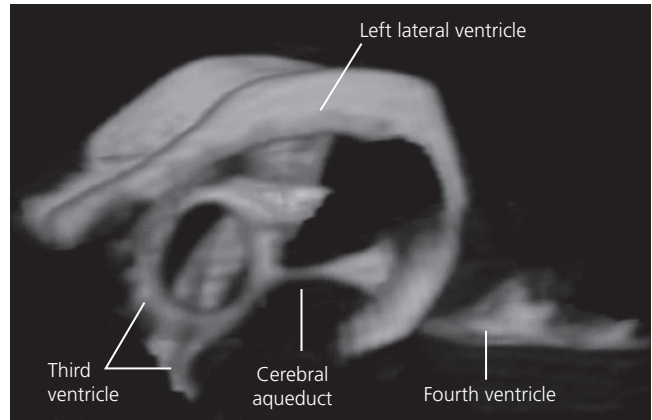
### Extracellular environment of the CNS

- 1 What are the blood–CSF and blood–brain barriers? Where are they located?
- 2 What transport mechanisms are involved in production of the CSF by the choroid plexus?
- 3 Explain the formation, circulation, and function of the CSF.
- 4 What structure represents the blood–brain barrier?
- 5 What transport mechanisms are involved in the blood–brain barrier?
- 6 List the areas of the brain where the blood–brain barrier is absent and explain the reason.

Neurons and neuroglia require a chemically stable environment. Thus, the brain receives only the essential materials from the blood and CSF. Two structures acting as gatekeepers to the brain's interior are (i) the **choroid epithelium** of the choroid plexus that acts as the blood–CSF barrier and (ii) the **capillaries** of the nervous tissue that act as the blood–brain barrier.

#### Blood–CSF barrier

The choroid plexus is present in the lateral, third and fourth ventricles (Figure 1.6). It is formed by invagination of the pia mater covered with choroid epithelial cells on the surface facing the ventricle. Vasculature of the pia mater follows the choroid plexus, providing rich capillary networks. The choroid epithelial cells are modified ependymal cells (they have microvilli instead of cilia on the apical surface). The capillary endothelium of the choroid plexus has many fenestrations in its wall, allowing passage of many small molecules. In contrast, choroid epithelial cells are sealed together by a tight junction that prevents the passage of water-soluble molecules into the CSF. Tight junctions are the anatomical basis of the **blood–CSF barrier** (Figure 1.7). Thus, **choroid epithelial cells** play a key role in regulating what can enter and leave the CNS tissue, maintaining an optimal environment for neurons and neuroglia. The choroid plexus relies on carrier proteins to transport essential molecules. Carrier proteins are located on the basal surface of the choroid epithelial cells. Essential molecules are released into the ventricle through the apical surface of the choroid epithelial cells, probably by facilitated diffusion. The CSF is also important for removing waste products from the CNS. Waste products removed from the CNS are drained into the dorsal sagittal sinus via the arachnoid villi.

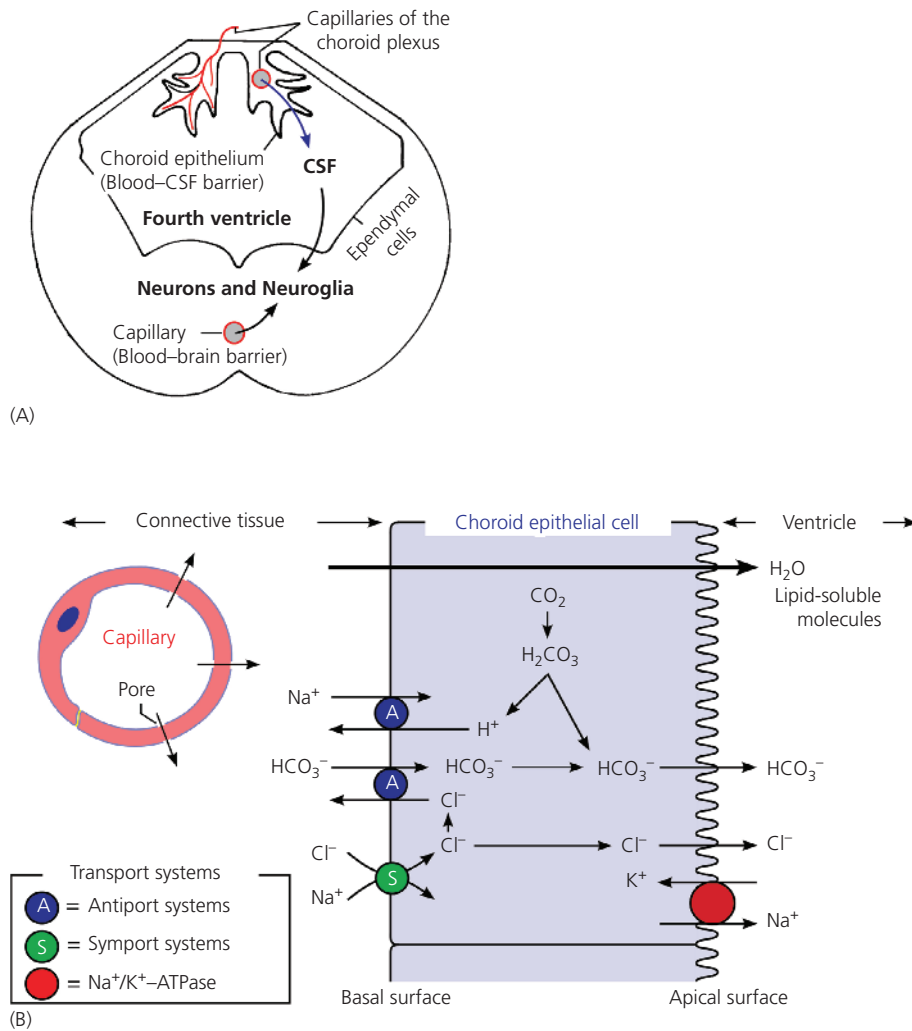


**Figure 1.6** MRI reconstruction of the ventricles of a dog showing the lateral ventricles, third ventricle, cerebral aqueduct, and fourth ventricle. Dr A. Zur Linden, Iowa State University College of Veterinary Medicine. Reproduced with permission from Dr A. Zur Linden.

#### Clinical correlations

Certain antibiotics (e.g., penicillin and most cephalosporin antibiotics) are actively removed from the CSF. Thus, the concentration of penicillin in CSF is about 1% of that in the blood. Interestingly, the choroid plexus under inflammatory conditions (e.g., meningitis) becomes leaky, resulting in a partial breakdown of the blood–CSF barrier. Consequently, the concentration of penicillin in CSF increases to 20% or more of that in the blood, preventing further bacterial growth or even killing bacteria. As inflammation subsides, the choroid plexus regains the function of the blood–CSF barrier and resumes removal of penicillin from CSF, allowing the possibility of a relapse of bacterial growth. Therefore, use of antibiotics that are not actively removed from the CSF (e.g., ceftriaxone with broad-spectrum activity against Gram-positive and Gram-negative bacteria) must be considered for treating many types of meningitis.

**Cerebrospinal fluid** is 99% water, which the choroid plexus secretes into the ventricles by creating ion gradients on both apical and basal surfaces of choroid epithelial cells (Figure 1.7). Water in the choroid epithelial cells dissociates into hydrogen ( $H^+$ ) and hydroxyl ( $OH^-$ ) ions.  $OH^-$  combines with intracellular  $CO_2$  produced by cell metabolism to form bicarbonate ions ( $HCO_3^-$ ). At the basal surface of the cells,  $H^+$  is exchanged for extracellular sodium ions ( $Na^+$ ) from the blood.  $Na^+$  is pumped out through the apical surface into the ventricles. The flux of  $Na^+$  results in an excess positive charge in the ventricles. To neutralize this excess positive charge, chloride ions ( $Cl^-$ ) and  $HCO_3^-$  move into the ventricles. Water also diffuses into the ventricles to maintain osmotic balance. These processes maintain water and concentration of ions in the CSF appropriate for the brain and spinal cord. Water and ions are not the only substances that the CNS must obtain from the blood. The majority of micronutrients



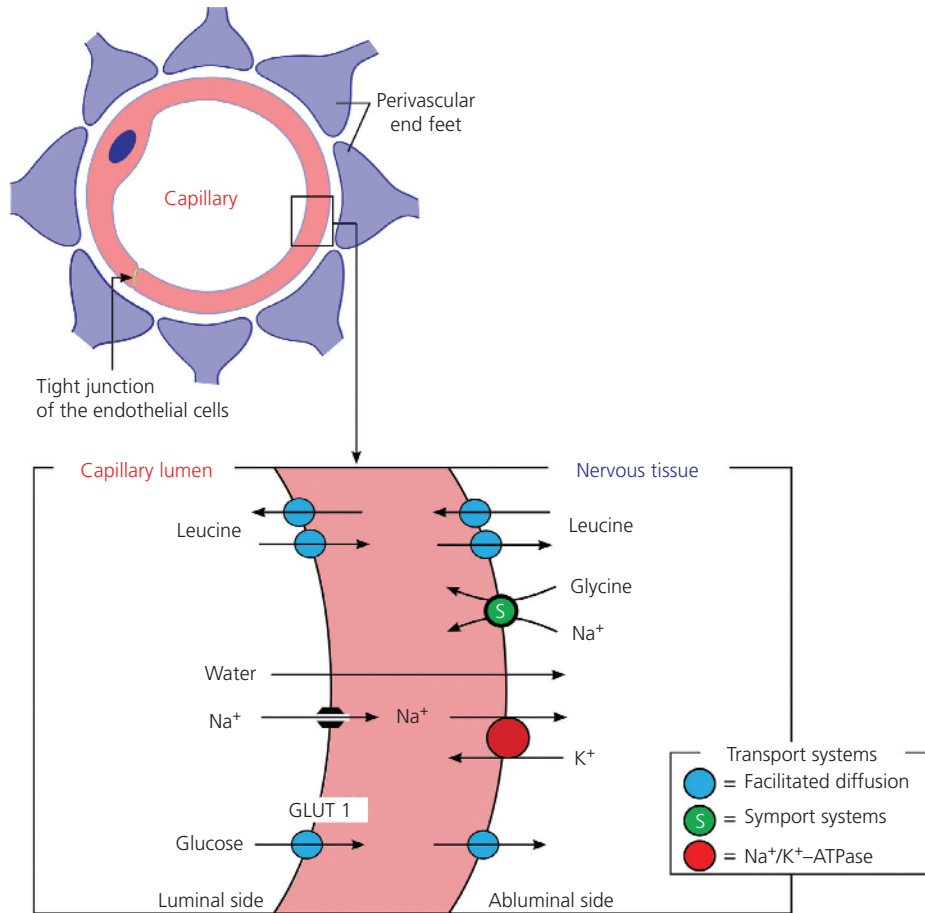
**Figure 1.7** (A) Neurons and neuroglial cells receive essential materials via two routes. Capillaries in the choroid plexus provide micronutrients, whereas interstitial capillaries provide oxygen and substances that the CNS consumes rapidly and in large amounts. The fourth ventricle is exaggerated here and not proportional to the size of the medulla oblongata. (B) The capillaries in the choroid plexus do not act as the blood–CSF barrier, as they are fenestrated (i.e., many pores) and intercellular gaps between endothelial cells are not tight as those found in capillaries of the CNS. As a result, molecules easily cross the capillary endothelial cell of the choroid plexus. The blood–CSF barrier is provided by the choroid epithelial cells, which are joined together by tight junctions. Microvilli of the choroid epithelial cells are present on the ventricular side of the epithelium. The choroid plexus produces CSF by diffusion, facilitated diffusion, and active transport systems. The choroid plexus epithelium also transports metabolites from CSF to blood (not shown).

(substances that are essential to the brain but only needed in relatively small amounts) come from the CSF. Micronutrients include vitamin B<sub>6</sub> (pyridoxine), folates (members of vitamin B-complex class) and vitamin C. In contrast, nutrients (glucose, amino acids, lactate) that the CNS requires in large amounts are delivered directly into the interstitial fluid by the capillary endothelium. This process depends on a facilitated-diffusion system.

### Blood-brain barrier

It is known that a dye such as trypan blue, injected intravenously, stains all tissues of the body except the brain and spinal cord. Animals do not show any adverse effects from this

procedure. However, when the dye is injected into the ventricle, the whole brain is diffusely stained and animals suffer from neurological problems. Clearly, the central nervous tissue has some barrier against the passage of a circulating dye, and this barrier is referred to as the blood–brain barrier (Figure 1.8). The site of the blood–brain barrier was shown by use of a tracer, horseradish peroxidase (HRP). HRP injected into the ventricle easily enters the extracellular spaces of the brain by crossing the ependymal cells. Although HRP in the brain passes through the capillary basement membrane, it is prevented from crossing the capillary wall into the lumen. However, there are a few specialized areas in the brain that allow entry of dyes or HRP. These nonbarrier regions include the choroid plexus, hypophys,



**Figure 1.8** Transport of molecules across capillaries of the CNS. Continuous tight junctions of endothelial cells restrict the diffusion of large and small solutes across the endothelial cells. The perivascular end feet encircle the capillary. Transport carriers for essential amino acids and glucose facilitate their movement into the CNS. Active transport systems moves small nonessential amino acids from brain to blood.  $\text{Na}^+$  is transported from blood to the CNS by  $\text{Na}^+$  transporters on the luminal membrane and  $\text{Na}^+/\text{K}^+$ -ATPase on the abluminal membrane. This  $\text{Na}^+$  movement drives transport of water into the CNS.

median eminence, pineal gland, and area postrema. Capillaries in these areas are fenestrated, which is essential for these areas to carry out their function (e.g., release of hormones into the circulation, monitoring circulating molecules). Thus, capillaries are the factor that restricts what can enter the brain from the blood.

The morphological basis of the blood–brain barrier is established by the electron microscope. Capillaries of the CNS are associated with three unique features: (i) continuous **tight junctions** that seal neighboring endothelial cells, (ii) absence of **fenestrations** and (iii) only a small number of **pinocytotic vesicles**. Although capillary endothelium is the structural basis of the blood–brain barrier, such a property appears to be maintained by astrocytes that form perivascular end feet around the entire outer surface of the capillary endothelium (Figure 1.8). This association suggests that the interaction between astrocytes and endothelial cells is important for the maintenance of

the blood–brain barrier. Thus, it is not surprising to see the absence of normal astrocyte–endothelial cell relationships in the nonbarrier regions of the brain mentioned above and in brain tumors. The transcellular transport is the only way for any substance in the blood to enter the CNS. The plasma membrane is made of a lipid bilayer. It is not permeable to charged molecules and most polar molecules such as sugars and amino acids. Anions in water are attracted electrostatically to the hydrogen atom of water, whereas cations are attracted to the oxygen atom of water. Such attraction of ions to water molecules imposes a barrier for ions to pass through the hydrophobic lipid bilayer of membrane. Thus, lipophilic substances (e.g., nicotine and ethanol) are very permeable and their transport through the endothelial cells is only limited by blood flow. Gases (e.g.,  $\text{CO}_2$ ,  $\text{O}_2$ ,  $\text{N}_2\text{O}$ ) diffuse rapidly into brain. Water also crosses freely in either direction through the membrane by diffusion as the osmolality of the plasma changes.

The brain needs certain water-soluble nutrients, such as glucose or certain essential amino acids. However, water-soluble compounds are restricted from passing through the blood–brain barrier into the brain. Glucose is a vital source of energy in the brain and its transport depends on a specific glucose carrier (GLUT 1) in the capillary endothelial cells. GLUT 1 is a facilitative transporter located at both the luminal and the abluminal side of the endothelial membrane. Facilitated diffusion carried out by the carriers does not consume energy. Facilitated diffusion moves molecules in both directions across the membrane, but the net flow is from the side of higher concentration to that of lower concentration. Since glucose is rapidly consumed in the CNS, the glucose concentration in interstitial fluid is normally lower than in blood plasma. As a result, the net flow of glucose across the blood–brain barrier is from blood to interstitial fluid. Specific carriers have substrate specificity. Thus, the carriers that transport D-glucose do not transport the L-enantiomer.

Large neutral amino acids (e.g., phenylalanine, leucine, tyrosine, isoleucine, valine, tryptophan, methionine, histidine, and L-dopa) are transported by facilitated diffusion both on the luminal and abluminal sides of the endothelial cells. Some of them, for example tryptophan, are precursors for neurotransmitters (serotonin, melatonin) synthesized in the CNS. Serotonin is involved in mood and sleep and melatonin regulates the sleep–wake cycle (circadian rhythm). Smaller neutral amino acids such as glycine, alanine, serine, cysteine, proline, and  $\gamma$ -aminobutyric acid (GABA) are synthesized in the CNS. These amino acids are also transported primarily from the brain to the circulation. Their transport requires an energy-dependent and  $\text{Na}^+$ -dependent symport carrier located at the abluminal side of the endothelial cell membrane.  $\text{Na}^+/\text{K}^+$ -ATPase located on the abluminal endothelial membrane provides the energy to drive the  $\text{Na}^+$  and amino acid symport carrier by maintaining high extracellular  $\text{Na}^+$  concentration in the CNS. Ion channels are also present in the luminal endothelial membrane. These ion channels and  $\text{Na}^+/\text{K}^+$ -ATPase work together to remove  $\text{K}^+$  from the interstitial fluid of the CNS in order to maintain a constant  $\text{K}^+$  concentration.

It appears that essential amino acids which are precursors for catecholamines (epinephrine and norepinephrine synthesized from tyrosine) and indolamine (e.g., serotonin and melatonin synthesized from tryptophan) are transported into the CNS. On the other hand, amino acids that are synthesized in the CNS and which function as neurotransmitters are not just restricted from crossing the blood–brain barrier into the CNS, but are transported out of the CNS. This lopsided transport across the blood–brain barrier may ensure that neurotransmitters will not accumulate in the brain, preventing the potential neurotoxic glutamate effect and unwanted inhibition of neurons by glycine and GABA.

### Clinical correlations

Water crosses the membrane freely in either direction by diffusion. This property of water across the membrane can be clinically useful in osmotherapy. For example, mannitol,  $\text{C}_6\text{H}_8(\text{OH})_6$ , is poorly permeable and intravenous administration of mannitol osmotically dehydrates the brain. Thus, mannitol can be used to reduce dangerously elevated intracranial pressure (e.g., after head trauma). Mannitol is also used experimentally to deliver drugs to the CNS by temporarily opening the blood–brain barrier. This osmotic disruption approach uses a concentrated dose of mannitol to remove fluid from the brain's endothelial cells, which causes endothelial cells to shrink and the tight junctions to open. However, the temporary opening of the blood–brain barrier is only applicable in disorders that do not require long-term treatment.

The blood–brain barrier is essential for maintaining stable functions of the CNS. The barrier imposed by the capillary endothelium ensures that any changes in nutrients, ions, and hormones do not directly influence synaptic functions. Unfortunately, the strict criteria set by the barrier applies equally to therapeutic drugs. The lipophilic antibiotic chloramphenicol crosses the blood–brain barrier without problems, but the highly hydrophilic penicillin is prevented from crossing the barrier. A high proportion (over 95%) of large-molecule drugs do not cross the blood–brain barrier, which includes all the products of biotechnology, recombinant proteins, and monoclonal antibodies. Thus, most drugs that are effective in the treatment of systemic diseases are not effective for treating CNS diseases. It is highly desirable that drugs are developed which can either directly or indirectly bypass the blood–brain barrier. Fortunately, inflammation associated with certain diseases affects the blood–brain barrier by increasing the permeability of endothelial membranes to certain antibiotics, allowing drugs to enter the CNS. As the inflammation decreases, entrance of the antibiotic also decreases, lowering the effectiveness of treatment.

### Self-evaluation

Answers can be found at the end of the chapter.

- Dendrites of neurons receive signals from other neurons.
  - True
  - False
- Neurons that have one axon and numerous dendrites are classified as:
  - Bipolar neuron
  - Multipolar neuron
  - Unipolar neuron
- Axon hillock is a site that generates action potentials.
  - True
  - False
- Neuroglia that is part of the choroid plexus comprises:
  - Astrocytes
  - Ependymal cells
  - Microglia
  - Oligodendrocytes

- 5 Which statement about astrocytes are not correct?  
 A Astrocytes form the choroid plexus  
 B Astrocytes transport glucose from capillaries to neurons  
 C Astrocytes form perivascular end feet  
 D Astrocytes continue dividing after birth  
 E Astrocytes prevent intercellular accumulation of the neurotransmitter glutamate
- 6 The myelin sheath:  
 A Is made by oligodendrocytes in the PNS  
 B Is made by Schwann cells in the CNS  
 C Slows the nerve impulse traveling along axons  
 D Enables faster conduction velocity
- 7 A nerve fiber is made of:  
 A An axon only  
 B An axon and Schwann cells.  
 C An axon and endoneurium  
 D An axon and epineurium
- 8 Leucine is transported by facilitated diffusion at the blood–brain barrier.  
 A True  
 B False
- 9 What structure represents the blood–brain barrier?  
 A Choroid plexus  
 B Microglia  
 C Endothelial cells  
 D Astrocytes  
 E Meninges
- 10 Nerve fibers classified as A $\alpha$  are larger in diameter and faster in conduction than those fibers classified as C fibers.  
 A True  
 B False
- 11 Axons in the CNS are myelinated by:  
 A Astrocytes  
 B Schwann cells  
 C Ependymal cells  
 D Oligodendrocytes
- 12 Na<sup>+</sup>/K<sup>+</sup>-ATPase is located on which membrane of endothelial cells?  
 A Luminal  
 B Abluminal
- 13 Glucose in the CNS is transported by:  
 A Simple diffusion  
 B GLUT 1  
 C Facilitated diffusion  
 D Na<sup>+</sup>-dependent symport carrier  
 E Na<sup>+</sup>/K<sup>+</sup>-ATPase
- 14 The choroid plexus produces the CSF.  
 A True  
 B False
- 15 The CSF in the third ventricle enters the fourth ventricles via cerebral aqueduct.  
 A True  
 B False
- 16 What represents the blood–CSF barrier?  
 A Meninges  
 B Capillary endothelium of the choroid plexus  
 C Perivascular end feet  
 D Choroid epithelium  
 E Astrocytes
- 17 The blood–brain barrier is absent in the:  
 A Spinal cord  
 B Cerebellum  
 C Choroid plexus  
 D Area postrema  
 E Two of the above

### Suggested reading

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### Answers

- |     |      |
|-----|------|
| 1 A | 10 A |
| 2 B | 11 D |
| 3 A | 12 B |
| 4 B | 13 B |
| 5 A | 14 A |
| 6 D | 15 A |
| 7 B | 16 D |
| 8 A | 17 E |
| 9 C |      |