# Alterations in Neuromuscular Function

Effective motor function requires that muscles move and that the mechanics of their movement be programmed in a manner that provides for smooth and coordinated movement. In some cases, purposeless and disruptive movements can be almost as disabling as relative or complete absence of movement.

THE ORGANIZATION AND CONTROL OF MOTOR FUNCTION

As with other parts of the nervous system, the motor systems are organized in functional hierarchy, with each concerned with levels of function (Fig. 38-1). The highest level of function, which occurs at the level of the frontal cortex, is concerned with the purpose and planning of the movement.[1] The lowest level of the hierarchy occurs at the level of the spinal cord, which contains the basic reflex circuitry needed to coordinate the function of the motor units involved in the planned movement. Several anatomically distinct pathways project in parallel to the spinal cord from the higher motor centers. Above the spinal cord is the brain stem, and above the brain stem is the cerebellum and basal ganglia, structures that modulate the actions of the brain stem systems. Overseeing these supraspinal structures are the motor centers in the cerebral cortex.

The Motor Unit

The major effects of the elaborate processing of movement information that takes place in the brain has to do with contraction of skeletal muscles. The neurons that control skeletal
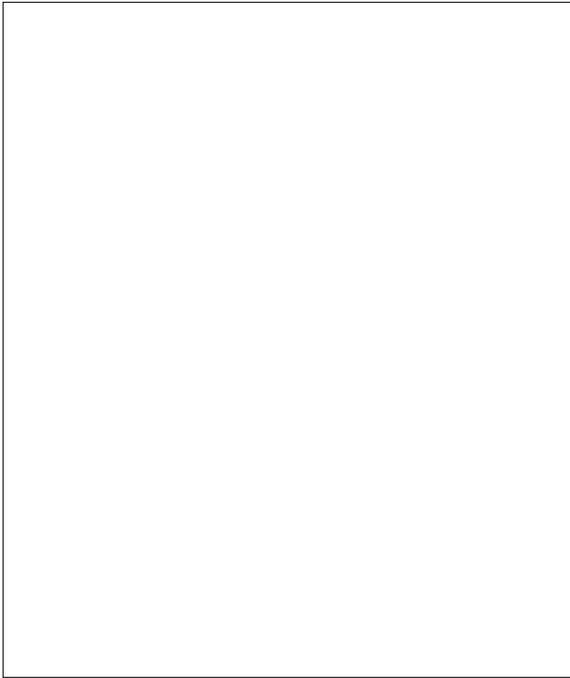
■ **FIGURE 38-1** ■ The motor control system. The final common pathway transmits all central nervous system commands to the skeletal muscles. This path is influenced by sensory input from the muscle spindles and tendon organs (*dashed lines*) and descending signals from the cerebral cortex and brain stem. The cerebellum and basal ganglia influence the motor function indirectly, using brain stem and cortical pathways.

muscle contraction are referred to as *motoneurons* or sometimes as *alpha motoneurons*. A motor unit consists of one motoneuron and the group of muscle fibers it innervates in a skeletal muscle. The motoneurons supplying a motor unit are located in the ventral horn of the spinal cord and are called *lower motoneurons* (LMNs) (Fig. 38-2). The synapse between a LMN and the muscle fibers of a motor unit is called the *neuromuscular junction*. Upper motoneurons (UMNs), which exert control over LMNs, project from the motor strip in the cerebral cortex to the ventral horn of the spinal cord and are fully contained within the central nervous system (CNS).

Axons of the LMNs exit the spinal cord at each segment to innervate skeletal muscle cells, including those of the limbs, back, abdomen, and chest. Each LMN undergoes multiple branching, making it possible for a single LMN to innervate 10 to 2000 muscle cells. In general, large muscles—those containing hundreds or thousands of muscle cells and providing gross motor movement—have large motor units. This sharply contrasts with those that control the hand, tongue, and eye movements, for which the motor units are small and permit very discrete control.

In addition to the output from LMNs that innervate the motor unit, the body uses information from a vast array of sensory input to ensure the generation of correct patterns of muscle activity. Much of this information goes to spinal cord reflexes that control muscle tone and coordinate the movement of the extensor and flexor muscles used in walking and other motor activities.
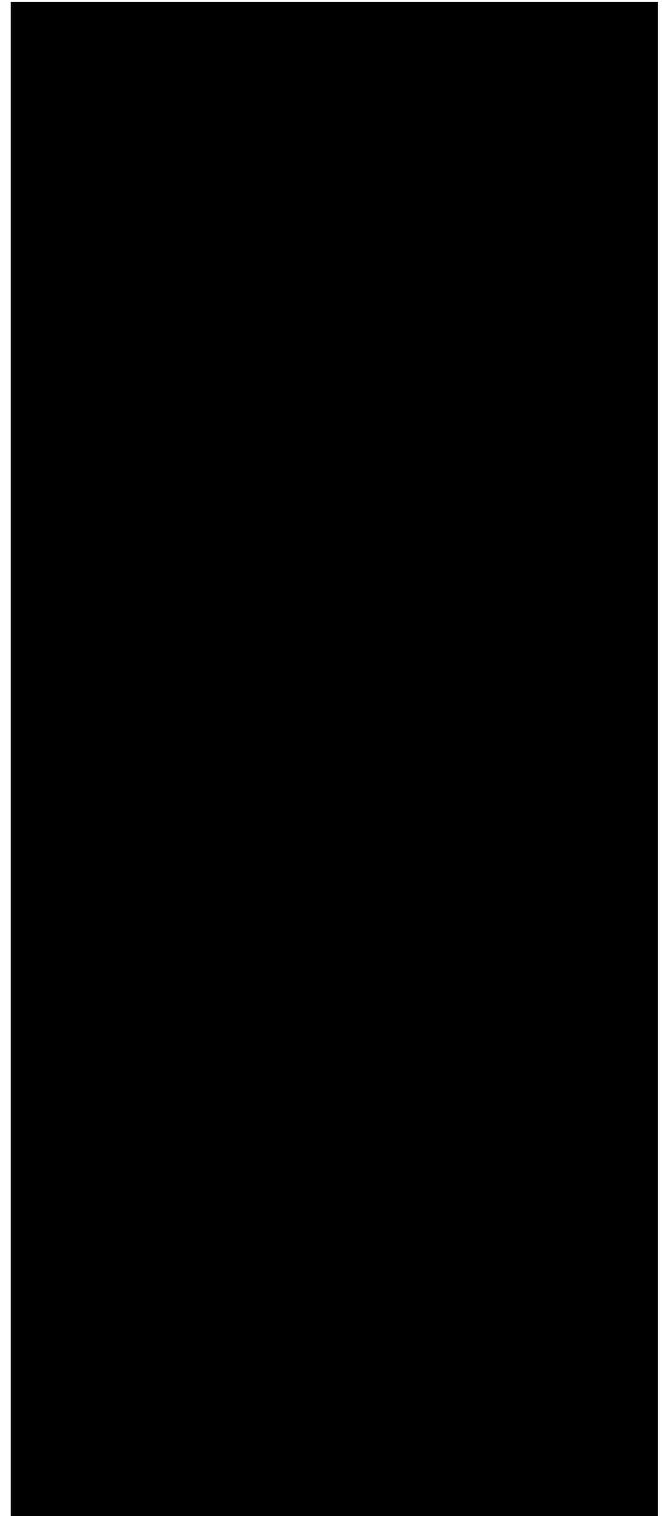
The Motor Cortex

Delicate, skillful, intentional movement of distal and especially flexor muscles of the limbs and the speech apparatus is initiated and controlled from the motor cortex located in the posterior part of the frontal lobe. It consists of the primary, premotor, and supplementary motor cortex[2] (Fig. 38-3). These areas receive information from the thalamus and the somesthetic (sensory) cortex and indirectly from the cerebellum and basal ganglia.

KEY CONCEPTS

MOTOR SYSTEMS

- Motor systems require upper motoneurons (UMNs) that project from the motor cortex to the brain stem or spinal cord, where they directly or indirectly innervate the lower motoneurons (LMNs) of the contracting muscles; sensory feedback from the involved muscles that is continuously relayed to the cerebellum, basal ganglia, and sensory cortex; and a functioning neuromuscular junction that links nervous system activity with muscle contraction.

- Input from the basal ganglia and cerebellum provides the background for the more crude, supportive movement patterns.

- The efficiency of the movement by the motor system depends on a background of muscle tone provided by the stretch reflex and vestibular system input to maintain stable postural support.

The *primary motor cortex* (area 4), also called the *motor strip*, is located on the rostral surface and adjacent portions of the central sulcus. The primary motor cortex controls discrete muscle movement sequences and is the first level of descending control for precise movements. The neurons in the primary motor cortex are arranged in a somatotopic array or distorted map of the body called the *motor homunculus* (Fig. 38-4).[3] The body parts that require the greatest dexterity have the largest cortical areas devoted to them. More than one half of the primary motor cortex is concerned with controlling the muscles of the hands, of facial expression, and of speech.[2]

The premotor cortex (areas 6 and 8), which is located just anterior to the primary motor cortex, sends some fibers into the corticospinal tract but mainly innervates the primary motor strip. A movement pattern to accomplish a particular objective, such as throwing a ball or picking up a fork, is programmed by the prefrontal association cortex and associated thalamic nuclei. The *supplementary motor cortex*, which contains representations of all parts of the body, is located on the medial surface of the hemisphere (areas 6 and 8) in the premotor region. It is intimately involved in the performance of complex, skillful movements that involve both sides of the body.

The primary motor cortex contains many layers of pyramid-shaped output neurons that project to the same side of the cortex (*i.e.*, premotor and somesthetic areas), project to the opposite side of the cortex, or descend to subcortical structures such as the basal ganglia and thalamus. The large pyramidal cells located in the fifth layer project to the brain stem and spinal cord. The axons of these UMNs project through the subcortical white matter and internal capsule to the deep surface of the brain stem, through the ventral bulge of the pons, and to the ventral surface of the medulla, where they form a ridge or pyramid (see Fig. 38-1). At the junction between the medulla and cervical spinal cord, 80% or more of the UMN axons cross the midline to form the lateral corticospinal tract in the lateral white matter of the spinal cord. This tract extends throughout the spinal
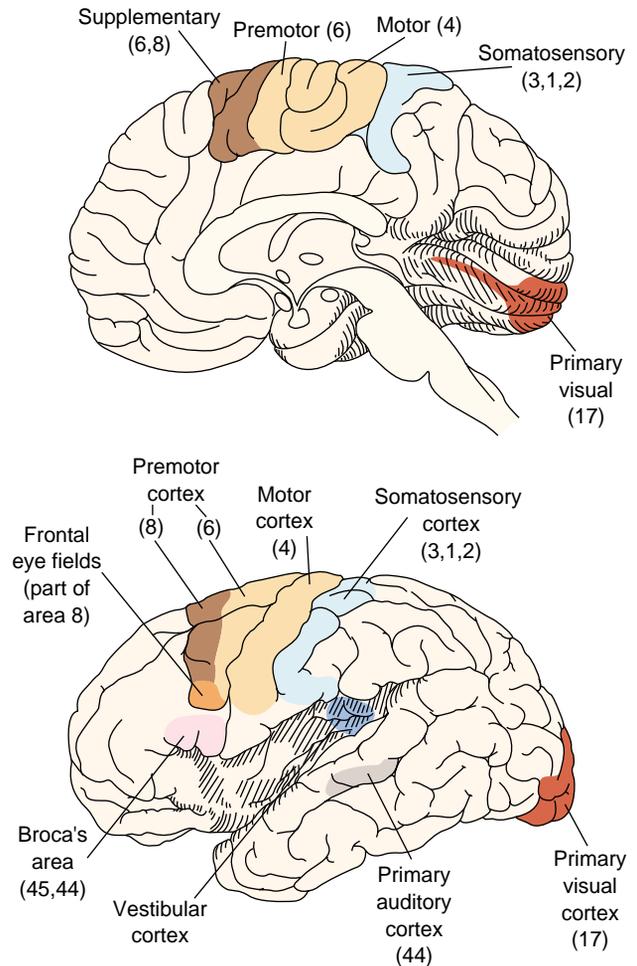
■ FIGURE 38-3 ■ Primary motor cortex. (**Top**) The location of the primary, premotor, and supplementary cortex on the medial surface of the brain. (**Bottom**) The location of the primary and premotor cortex on the lateral surface of the brain. (Courtesy of Carole Russell Hilmer, C.M.I.)

cord, with roughly 50% of the fibers terminating in the cervical segments, 20% in the thoracic segments, and 30% in the lumbosacral segments. Most of the remaining uncrossed fibers travel down the ventral column of the cord, mainly to cervical levels, where they cross and innervate contralateral LMNs.

By convention, motor tracts have been classified as belonging to one of two motor systems: the pyramidal and extrapyramidal systems. According to this classification system, the pyramidal system consists of the motor pathways originating in the motor cortex and terminating in the corticobulbar fibers in the brain stem and the corticospinal fibers in the spinal cord. The corticospinal fibers traverse the ventral surface of the medulla in a bundle called the *pyramid* before decussating or crossing to the opposite side of the brain at the medulla-spinal cord junction, thus the name *pyramidal system*. Other fibers from the cortex and basal ganglia also project to the brain stem reticular formation and reticulospinal systems, following a more ancient pathway to LMNs of proximal and extensor muscles. These fibers do not decussate in the pyramids, thus the name *extrapyramidal system*. Disorders of the pyramidal tracts (*e.g.*, stroke) are characterized by spasticity and paralysis and those affecting
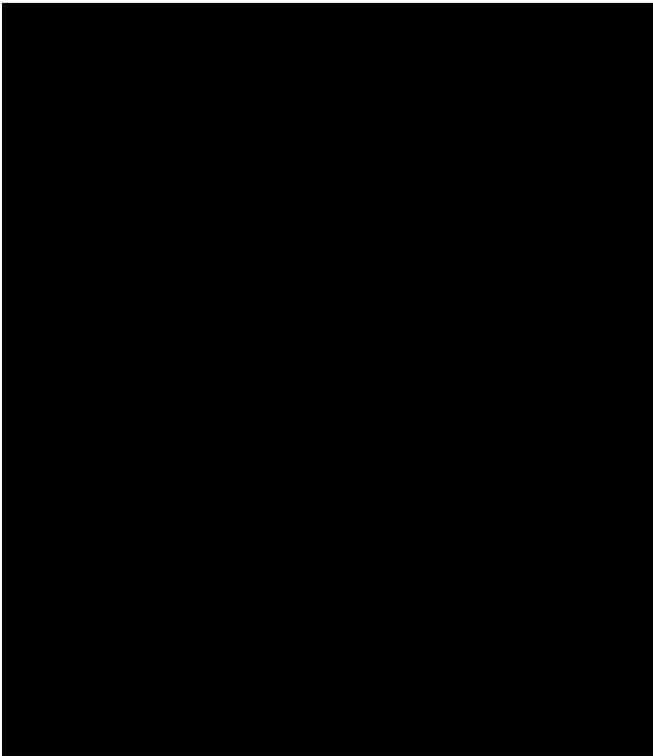
the extrapyramidal tracts (*e.g.*, Parkinson's disease) by involuntary movements, muscle rigidity, and immobility without paralysis. This classification is no longer used extensively. As increased knowledge regarding motor pathways has emerged, it has become evident that the extrapyramidal and pyramidal systems are extensively interconnected and cooperate in the control of movement.[1]

Spinal Reflexes

Reflexes are coordinated, involuntary motor responses initiated by a stimulus applied to peripheral receptors. Some reflexes, such as the flexion-withdrawal reflex, initiate movements to avoid hazardous situations; whereas others, such as the stretch or crossed-extensor reflex, serve to integrate motor movements so they function in a coordinated manner. The anatomic basis of a reflex consists of (1) an afferent neuron, (2) the connection or synapse with CNS interneurons that communicate with the effector neuron, and (3) the effector neuron that innervates a muscle. Reflexes are essentially "wired into" the CNS so that they are always ready to function; with training, most reflexes can be modulated to become parts of more complicated movements. A reflex may involve neurons in a single cord segment (*i.e.*, segmental reflexes), several or many segments (*i.e.*, intersegmental reflexes), or structures in the brain (*i.e.*, suprasegmental reflexes).

Myotatic or Stretch Reflex

The myotatic ("myo" from the Greek for "muscle," "tatic" from the Greek for "stretch") or stretch reflex controls muscle tone and helps maintain posture. Stretch reflexes can be evoked in many muscles throughout the body and are routinely tested (*e.g.*, knee-jerk reflex) during the clinical examination for the diagnosis of neurologic conditions. Disorders of muscle tone

caused by dysregulated function of the stretch reflex are seen in persons with conditions such as spinal cord injury and stroke.

The myotatic reflex uses specialized afferent sensory endings in skeletal muscles and tendons to relay information regarding the sense of body position, movement, and muscle tone to the CNS. Information from these sensory afferents is relayed to the cerebellum and cerebral cortex and is experienced as the sense of body movement and position (*proprioception*). To provide this information, the muscles and their tendons are supplied with two types of stretch receptors: muscle spindle receptors and Golgi tendon organs (Fig. 38-5A). The muscle spindles, which are distributed throughout the belly of a muscle, provide information about muscle length and rate of stretch. The *Golgi tendon organs* are found in muscle tendons and transmit information about muscle tension or force of contraction at the junction of the muscle and the tendon that attaches to bone. A likely role of the tendon organs is to equalize the contractile forces of the separate muscle groups, spreading the load over all the fibers to prevent the local muscle damage that might occur when small numbers of fibers are overloaded.

The muscle spindles consist of a group of specialized miniature skeletal muscle fibers called *intrafusal fibers* that are encased in a connective tissue capsule and attached to muscle fibers (*i.e.*, extrafusal fibers) of a skeletal muscle (Fig. 38-5A). An afferent sensory neuron, which spirals around the intrafusal fibers, transmits information to the spinal cord. The extrafusal fibers and the intrafusal fibers are innervated by motoneurons that reside in the ventral horns of the spinal cord. Extrafusal fibers are innervated by large alpha motoneurons that produce contraction of the muscle. The intrafusal fibers are innervated by gamma motoneurons that adjust the length of the intrafusal fibers to match that of the extrafusal fibers.

The intrafusal muscle fibers function as stretch receptors. When a skeletal muscle is stretched, the spindle and its intrafusal fibers are stretched, resulting in increased firing of its afferent fibers. The increased firing of the afferent neurons synaptically depolarizes the alpha motoneuron fibers. This causes the extrafusal muscle fibers to contract, thereby shortening the muscle. The knee-jerk reflex that occurs when the knee is tapped with a reflex hammer tests for the intactness of the myotatic reflex arc in the quadriceps muscle (Fig. 38-5B).

Axons of the spindle afferent neurons enter the spinal cord through the several branches of the dorsal root. Some branches end in the segment of entry, and others ascend in the dorsal column of the cord to the medulla of the brain stem. Segmental branches make connections, along with other branches, that pass directly to the anterior gray matter of the spinal cord and establish monosynaptic contact with each of the LMNs that have motor units in the muscle containing the spindle receptor. This produces an opposing muscle contraction. Another segmental branch of the same afferent neuron innervates an internuncial neuron that is inhibitory to motor units of antagonistic muscle groups. Inhibition of these muscle units helps in opposing muscle stretch. Branches of the afferent axon also ascend into the dorsal horn of the adjacent segments, influencing intersegmental reflex function. Ascending fibers from the stretch reflex ultimately provide information about muscle length to the cerebellum and cerebral cortex.

The role of afferent spindle fibers is to inform the CNS of the status of muscle length. When a skeletal muscle lengthens or
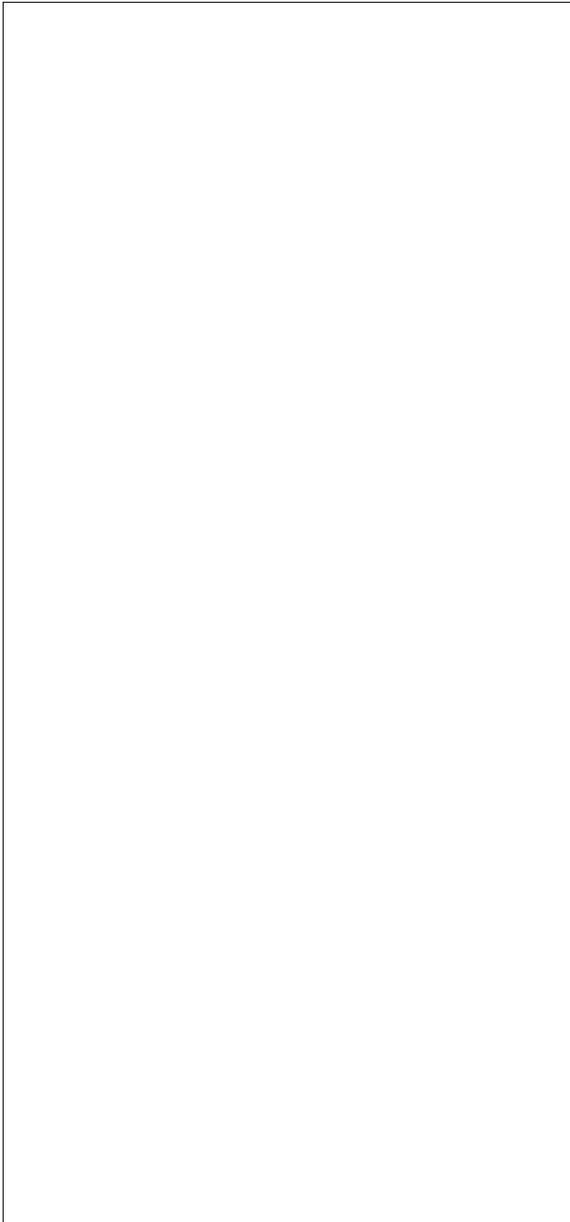
■ **FIGURE 38-5** ■ (**A**) Spinal cord innervation of the muscle spindles. Cell bodies from both the alpha motoneuron that innervates the extrafusal muscle fiber and the gamma motoneuron that innervates the intrafusal fiber reside in the ventral horn of the same segment of the spinal cord. (**B**) The knee-jerk reflex. Stretching of the extrafusal fiber by tapping with a reflex hammer leads to lengthening of the intrafusal fiber and increased firing of the type Ia afferent fiber. Impulses from the Ia fiber enter the dorsal horn of the spinal cord and make monosynaptic contact with the ventral horn alpha motoneuron supplying the extrafusal fibers in the quadriceps muscle. The resultant contraction (shortening) of the quadriceps muscle is responsible for the knee-jerk response.

shortens against tension, a feedback mechanism needs to be available for readjustment such that the spindle apparatus remains sensitive to moment-to-moment changes in muscle stretch, even while changes in muscle length are occurring. This is accomplished by the gamma motoneurons that adjust spindle fiber length to match the length of the extrafusal muscle fiber. Descending fibers of motor pathways synapse with and

simultaneously activate both alpha and gamma motoneurons so that the sensitivity of the spindle fibers is coordinated with muscle movement.

Central control over the gamma LMN mechanism permits increases or decreases in muscle tone in anticipation of changes in the muscle force required to oppose ongoing conditions, such as when weight is about to be lifted. The CNS, through its coordinated control of the muscle's alpha LMNs and the spindle's gamma LMNs, can suppress the stretch reflex. This occurs during centrally programmed movements, such as pitching a baseball, permitting the muscle to produce its greatest range of motion. Without this programmed adjustability of the stretch reflex, any movement is immediately opposed and prevented.

Crossed-Extensor Reflex

The crossed-extensor reflex, in which the limb on one side of the body extends as the limb on the other side relaxes, provides the basis for postural stability during walking (Fig. 38-6).[4] For example, when the crossed-extensor reflex produces relaxation of antigravity muscles (with flexion) of one leg as we walk, the contralateral component produces contraction and extension of the opposite leg. Intersegmental connections of the crossed-extensor reflex between the lumbar and cervical spinal segments also accounts for the swinging of the arms that accompanies walking.

Disorders of Muscle Tone and Movement

Disorders of Muscle Tone

In the muscles that are supporting body weight, the stretch reflex operates continuously, producing a continuous resistance to passive stretch called *muscle tone*. Muscle tone is evidenced by the resistance to passive movement around a joint. Disorders of skeletal muscle tone are characteristic of many nervous system pathologies. Any interruption of the myotatic reflex circuit by peripheral nerve injury, pathology of the neuromuscular junction and of skeletal muscle fibers, damage to the corticospinal system, or injury to the spinal cord or spinal nerve root results in disturbance of muscle tone. Muscle tone may be
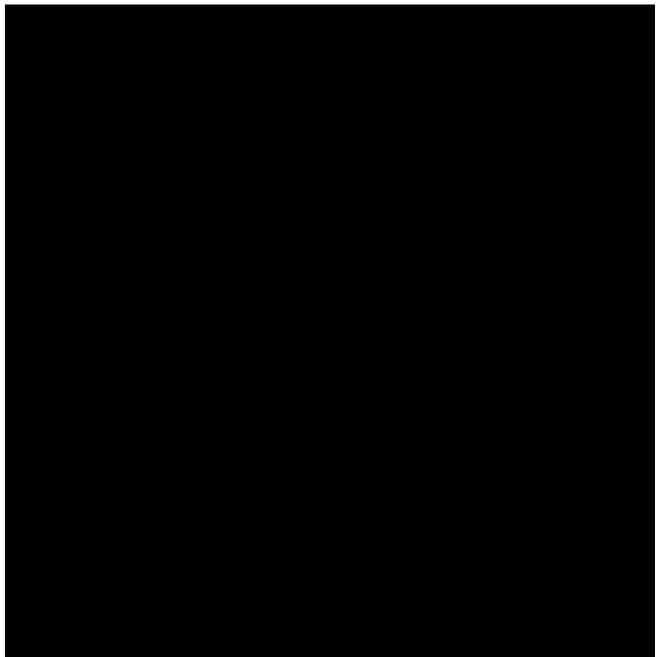
described as less than normal (hypotonia), absent (flaccidity), or excessive (hypertonia, rigidity, spasticity, or tetany).

Reduced excitability of the stretch reflex results in decreased muscle tone, or *hypotonia*, ranging from postural weakness to total flaccid paralysis. It can result from decreased function of the descending facilitatory systems controlling the gamma LMNs that innervate the muscle or damage to the stretch reflex or peripheral nerves innervating the muscle.

Hypertonia, or spasticity, is an abnormal increase in muscle tone. It can result from increased excitation or loss of inhibition of the spindle's gamma LMNs or changes in the segmental spinal cord circuitry controlling the stretch reflex. It is characterized by hyperactive tendon reflexes and an increase in resistance to rapid muscle stretch. Spasticity commonly occurs with UMN lesions such as those that exist after spinal shock in persons with spinal cord injury.

Rigidity is a greatly increased resistance to movements in all directions. It is caused by increased activation of the alpha LMNs innervating the extrafusal muscle fibers and does not depend on the dorsal root innervation of the intrafusal spindle fibers. It is seen in conditions, such as Parkinson's disease, in which descending CNS inhibition of alpha LMNs is impaired.

Clonus is the rhythmic contraction and alternate relaxation of a limb that is caused by suddenly stretching a muscle and gently maintaining it in the stretched position. It is seen in the hypertonia of spasticity associated with UMN lesions, such as spinal cord injury. It is caused by an oscillating stimulation of the muscle spindles that occurs when the spindle fibers are activated by an initial muscle stretch. This results in reflex contraction of the muscle and unloading of the spindle fibers with decreased afferent activity. The reduced spindle fiber activity causes the muscle to relax, which causes the spindle fiber to stretch again, and the cycle starts over.

Disorders of Muscle Movement

The suffix *plegia* comes from the Greek word for a blow, a stroke, or paralysis. The terms that are used to describe the extent and anatomic location of motor damage include *paralysis*, meaning loss of movement, and *paresis*, implying weakness or incomplete loss of muscle function. *Monoparesis* or *monoplegia* results from the destruction of pyramidal UMN innervation of one limb; *hemiparesis* or *hemiplegia*, both limbs on one side; *diparesis* or *diplegia* or *paraparesis* or *paraplegia*, both upper or lower limbs; and *tetraparesis* or *tetraplegia*, also called *quadriparesis* or *quadriplegia*, all four limbs[5] (Fig. 38-7). Paresis or paralysis can be further designated as of UMN or LMN origin.

Upper Motoneuron Lesions. A UMN lesion can involve any part of the CNS: the motor cortex, the internal capsule, or other brain structures through which the corticospinal or corticobulbar tracts descend, or the spinal cord. When the lesion is at or above the level of the pyramids, paralysis affects structures on the opposite side of the body. In UMN disorders involving injury to the L1 level or above, there is an immediate, profound weakness and loss of fine, skilled voluntary lower limb movement, reduced bowel and bladder control, and diminished sexual functioning, followed by an exaggeration of muscle tone. With UMN damage above C7, upper limb movement also is affected (see section on spinal cord injury).

With UMN lesions, the LMN spinal reflexes remain intact, but communication and control from higher brain centers are
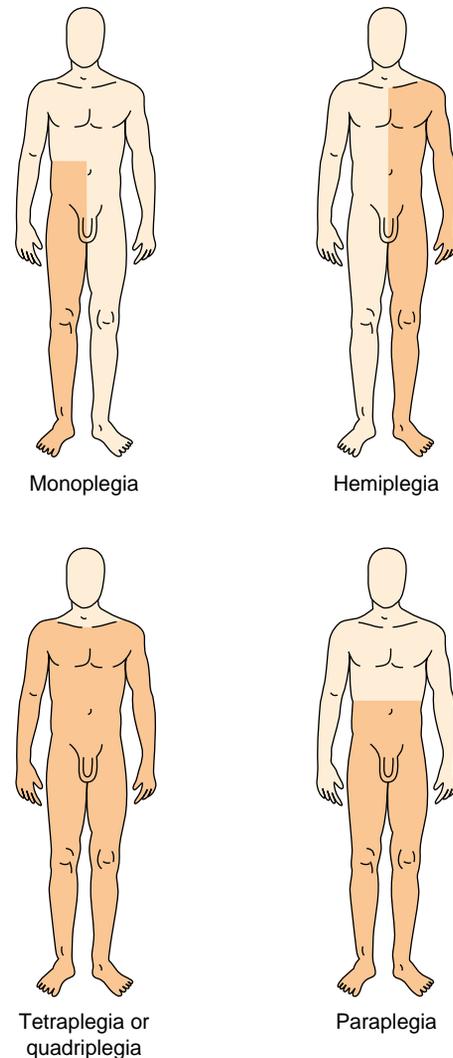
■ **FIGURE 38-7** ■ Areas of the body affected by monoplegia, hemiplegia, tetraplegia or quadriplegia, and paraplegia. The *shaded area* shows the extent of motor and sensory loss.

Monoplegia   Hemiplegia

Tetraplegia or   Paraplegia
quadriplegia

lost. Descending excitatory influences from the pyramidal system and some descending inhibitory influences from other cortical regions are lost after injury, resulting in immediate weakness accompanied by the loss of control of delicate, skilled movements. After several weeks, this weakness becomes converted to hypertonicity or spasticity, which is manifested by an initial increased resistance (stiffness) to the passive movement of a joint at the extremes of range of motion followed by a sudden or gradual release of resistance. The spasticity often is greatest in the flexor muscles of the upper limbs and extensor muscles of the lower limbs. Sometimes, a lesion of the pyramidal tract is less severe and results in a relatively minor degree of weakness. In this case, the finer and more skilled movements are most severely impaired.

Lower Motoneuron Lesions. In contrast to UMN lesions, in which the spinal reflexes remain intact, LMN disorders disrupt communication between the muscle and all neural input from spinal cord reflexes, including the stretch reflex, which maintains muscle tone.

KEY CONCEPTS

SPASTIC VERSUS FLACCID PARALYSIS

■ Afferent input from stretch receptors located in muscles and joints is incorporated into spinal cord reflexes that control muscle tone. The activity of the spinal cord reflexes that control muscle tone is constantly monitored and regulated by input from higher brain centers.

■ Upper motoneuron lesions that interrupt communication between the spinal cord reflexes and higher brain centers result in unregulated reflex activity, increased muscle tone, and spastic paralysis.

■ Lower motoneuron lesions that interrupt communication between the muscle and the spinal cord reflex result in a loss of reflex activity, decreased or absent muscle tone, and flaccid paralysis.

Infection or irritation of the cell body of the LMN or its axon can lead to hyperexcitability, which causes spontaneous contractions of the muscle units. These can be observed as twitching and squirming movements on the muscle surface, a condition called *fasciculations*. Toxic agents, such as the tetanus toxin, produce extreme hyperexcitability of the LMN, which results in continuous firing at maximum rate. The resultant sustained contraction of the muscles is called *tetany*. Tetany of muscles on both sides of a joint produces immobility or tetanic paralysis. When a virus, such as the poliomyelitis virus, attacks an LMN, it first irritates the LMN, causing fasciculations to occur. These fasciculations often are followed by death of LMNs. Weakness and severe muscle wasting or denervation atrophy result. If muscles are totally denervated, total weakness and total loss of reflexes, called *flaccid paralysis*, occurs.

With complete LMN lesions, the muscles of the affected limbs, bowel, bladder, and genital areas become atonic, and it is impossible to elicit contraction by stretching the tendons. One of the outstanding features of LMN lesions is the profound development of muscle atrophy. Damage to an LMN with or without spinal cord damage, often called *peripheral nerve injury*, may occur at any level of the spinal cord. For example, a C7 peripheral nerve injury leads to LMN hand weakness only. All segments below the level of injury that have intact LMNs manifest UMN signs. Usually, injury to the spinal cord at the T12 level or below results in LMN injury and flaccid paralysis to all areas below the level of injury. This occurs because the spinal cord ends at the T12 to L1 level, and from this level, the spinal roots of the LMNs continue caudally in the vertebral canal as part of the cauda equina.

In summary, motor function involves the neuromuscular unit, spinal cord circuitry, brain stem neurons, the cerebellum, the basal ganglia, and the motor cortex. A motor unit consists of one LMN and the group of muscle fibers it innervates in the muscle. Delicate, skillful, intentional movement of distal and especially flexor muscles of the limbs and the

speech apparatus is initiated and controlled from the motor cortex located in the posterior frontal lobe. It consists of the primary, premotor, and supplementary motor cortex. These areas receive information from the thalamus and somesthetic cortex and, indirectly, from the cerebellum and basal ganglia. The UMNs in the motor cortex send their axons through the subcortical white matter and internal capsule and the deep surface of the brain stem to the ventral surface to the opposite side of the medulla, where they form a pyramid before crossing the midline to form the lateral corticospinal tract in the spinal cord.

Alterations in musculoskeletal function include muscle tone and movement. Muscle tone is maintained through the combined function of the muscle spindle system and the CNS centers that monitor and buffer UMN innervation of the LMNs. Hypotonia is a condition of less-than-normal muscle tone, and hypertonia or spasticity is a condition of excessive tone. Paresis refers to weakness in muscle function, and paralysis refers to a loss of muscle movement. UMN lesions produce spastic paralysis, and LMN lesions produce flaccid paralysis.

SKELETAL MUSCLE AND PERIPHERAL NERVE DISORDERS

Skeletal Muscle Disorders

Muscle Atrophy

Atrophy describes a decrease in muscle mass. Maintenance of muscle strength requires relatively frequent movements against resistance. When a normally innervated muscle is not used for long periods, the muscle cells shrink in diameter, and although the muscle cells do not die, they lose much of their contractile protein and become weakened. This is called *disuse atrophy*, and it occurs with conditions such as bed rest, application of a cast for fracture healing, and chronic illness.

The most extreme examples of muscle atrophy are found in persons with disorders, such as spinal cord injury, that deprive muscles of their innervation. This form is called *denervation atrophy*. Denervated muscles lose more than half their original bulk within 2 to 3 months.

Muscular Dystrophy

The term dystrophy refers to abnormal growth. *Muscular dystrophy* is a term applied to a number of genetic disorders that produce progressive deterioration of skeletal muscles because of mixed muscle cell hypertrophy, atrophy, and necrosis. They are primary diseases of muscle tissue and probably do not involve the nervous system. As the muscle undergoes necrosis, fat and connective tissue replace the muscle fibers, which increases muscle size and results in muscle weakness. The increase in muscle size resulting from connective tissue infiltration is called *pseudohypertrophy*. The muscle weakness is insidious in onset but continually progressive, varying with the type of disorder.

The most common form of muscular dystrophy is *Duchenne muscular dystrophy*, which has an incidence of approximately 3 cases per 100,000 male children. The disorder is inherited as a recessive single-gene defect on the X chromosome and is

transmitted from the mother to her male offspring (see Chapter 4).[6,7] Despite the X-linked inheritance pattern, about 30% of cases are new mutations and the mother is not the carrier.[8] Another form of muscular dystrophy, *Becker muscular dystrophy*, is similarly X-linked but manifests later in childhood or adolescence and has a slower course.

The Duchenne muscular dystrophy mutation results in a defective form of a very large protein associated with the muscle cell membrane, called *dystrophin*, which fails to provide the normal attachment site for the contractile proteins. As a result there is necrosis of muscle fibers, a continuous effort at repair and regeneration, and progressive necrosis (Fig. 38-8).[7]

Clinical Course. The postural muscles of the hip and shoulder are affected first in the Duchenne type muscular dystrophy, and the child usually has no problems until approximately 3 years of age, when frequent falling begins to occur. Imbalances between agonist and antagonist muscles lead to abnormal postures and the development of contractures and joint immobility. Scoliosis is common. Wheelchairs usually are needed at approximately 7 to 12 years of age.[8] The function of the distal muscles usually is preserved well enough that the child can continue to use eating utensils and a computer keyboard. The function of the extraocular nerves also is well preserved, as is the function of the muscles controlling urination and defecation. Incontinence is an uncommon and late event. Respiratory muscle involvement results in weak and ineffective cough, frequent respiratory infections, and decreasing respiratory reserve. Cardiomyopathy caused by involvement of cardiac muscle is a common feature of the disease. However, the severity of cardiac involvement does not necessarily correlate with skeletal muscle weakness. Some patients die at an early age of severe cardiomyopathy, whereas others maintain adequate cardiac function until the terminal stages of the disease. Death from respiratory and cardiac muscle involvement usually occurs in young adulthood.

Observation of the child's voluntary movement and a complete family history provide important diagnostic data for the disease. Serum levels of the enzyme creatine kinase, which

■ **FIGURE 38-8** ■ Duchenne muscular dystrophy: hematoxylin and eosin stain. A section of the vastus lateralis muscle shows necrotic muscle fibers, some of them invaded by macrophages. The endomysial septa are thickened, indicating fibrosis. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1422]. Philadelphia: Lippincott Williams & Wilkins)

leaks out of damaged muscle fibers, can be used to confirm the diagnosis. Muscle biopsy, which shows a mixture of muscle cell degeneration and regeneration and reveals fat and scar tissue replacement, is diagnostic of the disorder. Echocardiography, electrocardiography, and chest radiography are used to assess cardiac function. A specific molecular genetic diagnosis is possible by demonstrating the defective dystrophin in muscle biopsy tissue or by DNA analysis from the peripheral blood. The same methods of DNA analysis may be used on blood samples to establish carrier status in female relatives at risk, such as sisters and cousins. Prenatal diagnosis is possible as early as 12 weeks' gestation by sampling chorionic villi for DNA analysis (see Chapter 4).[8]

Management of the disease is directed toward maintaining ambulation and preventing deformities. Passive stretching, correct or counter posturing, and splints help to prevent deformities. Precautions should be taken to avoid respiratory infections. Although there have been exciting advances in identifying the gene and gene product involved in Duchenne muscular dystrophy, there is no known cure.

Neuromuscular Junction Disorders

The neuromuscular junction serves as a synapse between a motor neuron and a skeletal muscle fiber. It consists of the axon terminals of a motor neuron and a specialized region of the muscle membrane called the *end-plate*. The transmission of impulses at the neuromuscular junction is mediated by the release of the neurotransmitter acetylcholine from the axon terminals. Acetylcholine binds to specific receptors in the end-plate region of the muscle fiber surface to cause muscle contraction (Fig. 38-9). Acetylcholine is active in the neuromuscular junction only for a brief period, during which an action potential is generated in the innervated muscle cell. Some of the transmitter diffuses out of the synapse, and the remaining transmitter is rapidly inactivated by an enzyme called *acetylcholinesterase*. The rapid inactivation of acetylcholine allows repeated muscle contractions and gradations of contractile force.

A number of drugs and agents can alter neuromuscular function by changing the release, inactivation, or receptor binding of acetylcholine.[9] Curare acts on the postjunctional membrane of the motor end-plate to prevent the depolarizing effect of the neurotransmitter. Blocking of neuromuscular transmission by curare-type drugs is used during many types of surgical procedures to facilitate relaxation of involved musculature. Drugs such as physostigmine and neostigmine inhibit the action of acetylcholinesterase and allow acetylcholine released from the motoneuron to accumulate. These drugs are used in the treatment of myasthenia gravis.

Toxins from the botulism organism (*Clostridium botulinum*) produce paralysis by blocking acetylcholine release. Spores from the botulism organism may be found in soil-grown foods that are not properly cooked. A pharmacologic preparation of the botulism toxin (botulism toxin type A [Botox]) has become available for use in treating eyelid and eye movement disorders such as blepharospasm and strabismus. It also is used for treatment of spasmodic torticollis, spasmodic dysphonias (laryngeal dystonia), and other dystonias. The drug is injected into the target muscle using the electrical activity recorded from the tip of a special electromyographic injection needle to guide the
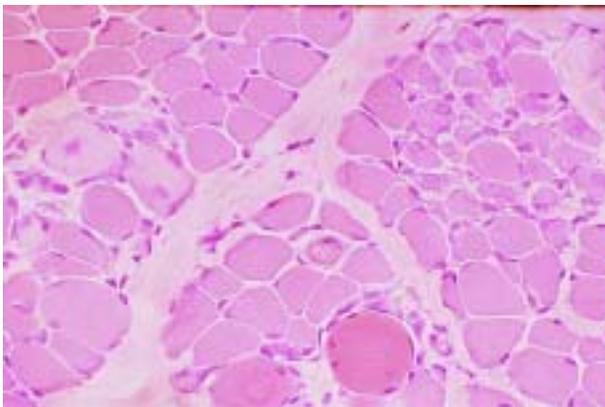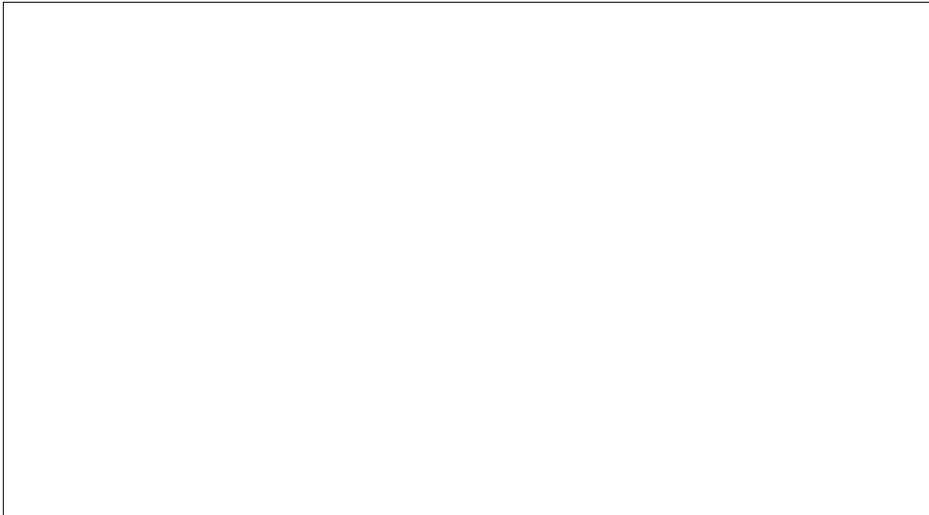
■ FIGURE 38-9 ■ Neuromuscular junction. (**A**) Acetylcholine (ACh) released from the motoneurons in the myoneural junction crosses the synaptic space to reach receptors that are concentrated in the folds of the end-plate of the muscle fiber. Once released, ACh is rapidly broken down by the enzyme acetylcholinesterase (AChesterase). (**B**) Decrease in ACh receptors in myasthenia gravis.

injection. The treatment is not permanent and usually needs to be repeated approximately every 3 months.

The organophosphates (*e.g.*, malathion, parathion) that are used in some insecticides bind acetylcholinesterase to prevent the breakdown of acetylcholine. They produce excessive and prolonged acetylcholine action with a depolarization block of cholinergic receptors, including those of the neuromuscular junction.[9] The organophosphates are well absorbed from the skin, lungs, gut, and conjunctiva of the eye, making them particularly effective as insecticides but also potentially dangerous to humans. Malathion and certain other organophosphates are rapidly metabolized to inactive products in humans and are considered safe for sale to the general public. The sale of other insecticides, such as parathion, which is not effectively metabolized to inactive products, has been banned. Other organophosphate compounds (*e.g.*, soman) were developed as "nerve gases"; if absorbed in high enough concentrations, they have lethal effects from depolarization block and loss of respiratory muscle function.

Myasthenia Gravis

Myasthenia gravis is a disorder of transmission at the neuromuscular junction that affects communication between the motoneuron and the innervated muscle cell. The disease may occur at any age, but the peak incidence occurs between 20 and 30 years of age and affects women more often than men. A smaller second peak occurs in later life and affects men more often than women.

Now recognized as an autoimmune disease, the disorder is caused by antibody-mediated loss of acetylcholine receptors in the neuromuscular junction (Fig. 38–9).[6,10] Although the exact mechanism that triggers the autoimmune response is unclear, it is thought to be related to abnormal T-lymphocyte function. Approximately two thirds of persons with myasthenia gravis also have thymic abnormalities, such as a thymoma (*i.e.*, thymus tumor) or thymic hyperplasia.[6,10]

In persons with myasthenia gravis who have fewer acetylcholine receptors in the postsynaptic membrane, each release of acetylcholine from the presynaptic membrane results in a lower-amplitude end-plate potential. This results in both muscle weakness and fatigability with sustained effort. Most commonly affected are the eye and preorbital muscles. Either pto-

sis caused by eyelid weakness or diplopia caused by weakness of the extraocular muscles is an initial symptom in approximately 50% of persons with the disease. The disease may progress from ocular muscle weakness to generalized weakness, including respiratory muscle weakness. Chewing and swallowing may be difficult, and persons with the disease often choose to eat soft foods and cereals, rather than meats and hard fruit. Weakness in limb movement usually is more pronounced in proximal than in distal parts of the extremity, so climbing stairs and lifting objects are difficult. As the disease progresses, the muscles of the lower face are affected, causing speech impairment. When this happens, the person often supports the chin with one hand to assist in speaking. In most persons, symptoms are least evident when arising in the morning, but they grow worse with effort and as the day proceeds.

Persons with myasthenia gravis may experience a sudden exacerbation of symptoms and weakness known as *myasthenia crisis*.[11] Myasthenia crisis occurs when muscle weakness becomes severe enough to compromise ventilation to the extent that ventilatory support and airway protection are needed. This usually occurs during a period of stress, such as infection, emotional upset, pregnancy, alcohol ingestion, cold, or after surgery. It also can result from inadequate or excessive doses of the anticholinesterase drugs used in treatment of the disorder.

Diagnosis and Treatment. The diagnosis of myasthenia gravis is based on history and physical examination, the anticholinesterase test, nerve stimulation studies, and an assay for acetylcholine receptor antibodies. The anticholinesterase test uses a drug that inhibits acetylcholinesterase, the enzyme that breaks down acetylcholine. When weakness is caused by myasthenia gravis, a dramatic transitory improvement in muscle function occurs when the drug used for the test is administered. Electrophysiologic studies can be done to demonstrate a muscle response to repetitive stimulation of motor nerves. An immunoassay test can be used to detect the presence of acetylcholine receptor antibodies circulating in the blood.

Treatment methods include the use of pharmacologic agents; immunosuppressive therapy, including corticosteroid drugs; management of myasthenic crisis; thymectomy; and plasmapheresis or intravenous immunoglobulin.[10] Pharmacologic treatment with reversible anticholinesterase drugs inhibits the

1 LINE

breakdown of acetylcholine at the neuromuscular junction by acetylcholinesterase. Corticosteroid drugs, which suppress the immune response, are used in cases of a poor response to anticholinesterase drugs and thymectomy. Immunosuppressant drugs (*e.g.*, azathioprine, cyclosporine) also may be used, often in combination with plasmapheresis.

Plasmapheresis removes antibodies from the circulation and provides short-term clinical improvement. It is used primarily to stabilize the condition of persons in myasthenic crisis or for short-term treatment in persons undergoing thymectomy. Intravenous immunoglobulin also produces improvement in persons with myasthenia gravis. Although the effect is temporary, it may last for weeks to months. The indications for its use are similar to those for plasmapheresis.

Thymectomy, or surgical removal of the thymus, may be used as a treatment for myasthenia gravis. Because the mechanism whereby surgery exerts its effect is unknown, the treatment is a matter of controversy. Thymectomy is performed in persons with thymoma, regardless of age, and in persons 50 to 60 years of age or older with recent onset of moderate disease.

Peripheral Nerve Disorders

The peripheral nervous system consists of the motor and sensory branches of the cranial and spinal nerves, the peripheral parts of the autonomic nervous system (ANS), and peripheral ganglia. Unlike the nerves of the CNS, peripheral nerves are fairly strong and resilient. They contain a series of connective tissue sheaths that enclose their nerve fibers. An outer fibrous sheath called the *epineurium* surrounds the medium to large nerves; inside, a sheath called the *perineurium* invests each bundle of nerve fibers, and within each bundle, a delicate sheath of connective tissue known as the *endoneurium* surrounds each nerve fiber (see Chapter 36, Fig. 36-3). Small peripheral nerves lack the epineurial covering. In its endoneurial sheath, each nerve fiber is invested by a segmented sheath of Schwann cells. The Schwann cells produce the myelin sheath that surrounds the peripheral nerves.

Peripheral Nerve Injury and Repair

Neurons exemplify the general principle that the more specialized the function of a cell type, the less able it is to regenerate. Although the entire neuron cannot be replaced, it often is possible for the dendritic and axonal cell processes to regenerate as long as the cell body remains viable.

When a peripheral nerve is destroyed by a crushing force or by a cut that penetrates the nerve, the portion of the nerve fiber that is separated from the cell body rapidly undergoes degenerative changes, whereas the central stump and cell body of the nerve often are able to survive. Because the cell body synthesizes the material required for nourishing and maintaining the axon, it is likely that the loss of these materials results in the degeneration of the separated portion of the nerve fibers. In crushing injuries in which the endoneurial tube remains intact, the outgrowing fiber will grow back down this tube to the structure that was originally innervated by the neuron (Fig. 38-10). However, it can take weeks or months for the regrowing fiber to reach its target organ and for communicative function to be re-established. More time is required for the Schwann cells to form new myelin segments and for the axon to recover its original diameter and conduction velocity. However, if the injury involves the severing of a nerve, the outgrowing branch must

LONG
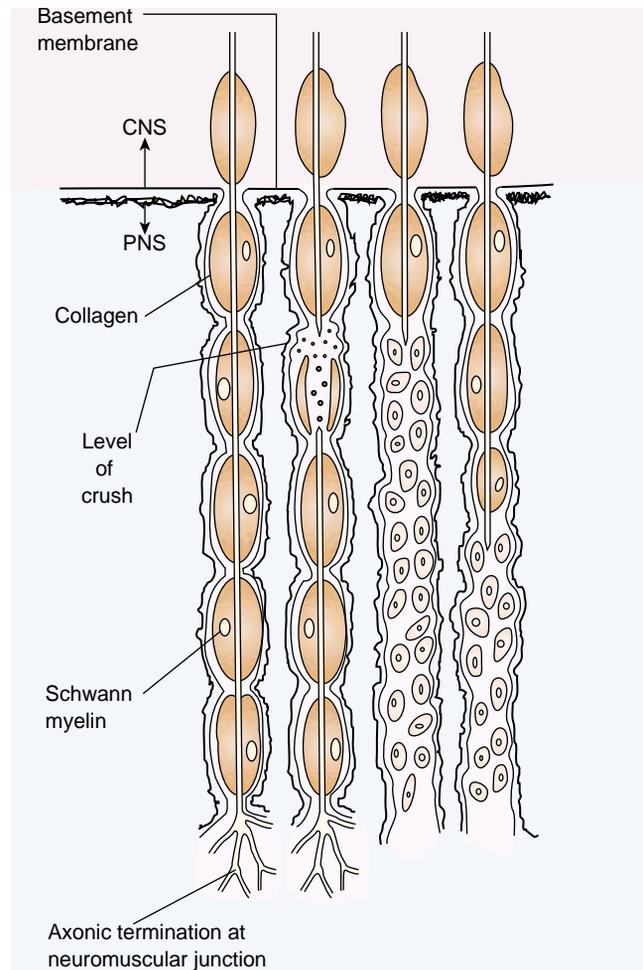
■ FIGURE 38-10 ■ Sequential stages in efferent axon degeneration and regeneration within its endoneurial tube, following peripheral nerve crush injury.

come in contact with its original endoneurial tube if it is to be reunited with its original target structure.

The successful regeneration of a nerve fiber in the peripheral nervous system depends on many factors. If a nerve fiber is destroyed relatively close to the neuronal cell body, the chances are that the nerve cell will die, and if it does, it will not be replaced. The degree of axonal regeneration that occurs after injury to a peripheral nerve also depends on the amount of scar tissue that develops at the site of injury and how quickly reinnervation occurs. If reinnervation occurs after the muscle cells have degenerated, no recovery is possible.

Perhaps the most difficult problem in the treatment of peripheral nerve injuries is the alignment of the proximal and distal endoneurial tubes so that a regenerating fiber can return down its former tube and innervate its former organ. Microscopic alignment of the cut edges during microsurgical repair results in improved success.

Peripheral Neuropathies

A peripheral neuropathy is any primary disorder of the peripheral nerves. The result usually is muscle weakness caused by LMN damage, with or without atrophy and sensory changes. The disorder can involve a single nerve (mononeuropathy) or multiple nerves (polyneuropathy).

Mononeuropathies. Mononeuropathies usually are caused by localized conditions such as trauma, compression, or infections that affect a single spinal nerve, plexus, or peripheral nerve trunk. Fractured bones may lacerate or compress nerves; excessively tight tourniquets may injure nerves directly or produce ischemic injury; and infections such as herpes zoster may affect a single segmental afferent nerve distribution.

Carpal Tunnel Syndrome. Carpal tunnel syndrome is an example of a compression-type mononeuropathy that is relatively common. It is caused by compression of the median nerve as it travels with the flexor tendons through a canal made by the carpal bones and transverse carpal ligament (Fig. 38-11). The condition can be caused by a variety of conditions that produce a reduction in the capacity of the carpal tunnel (*i.e.*, bony or ligament changes) or an increase in the volume of the tunnel contents (*i.e.*, inflammation of the tendons, synovial swelling, or tumors).[12] Carpal tunnel syndrome can be a feature of many systemic diseases such as rheumatoid arthritis, hyperthyroidism, acromegaly, and diabetes mellitus.[12] The condition can result from wrist injury; it can occur during pregnancy and use of birth control drugs; and it is seen in persons with repetitive use of the wrist (*i.e.*, flexion-extension movements and stress associated with pinching and gripping motions).

Carpal tunnel syndrome is characterized by pain, paresthesia, and numbness of the thumb and first two and one-half digits of the hand; pain in the wrist and hand, which worsens at night; atrophy of abductor pollicis muscle; and weakness in precision grip. All of these abnormalities may contribute to clumsiness of fine motor activity.

Transverse carpal ligament
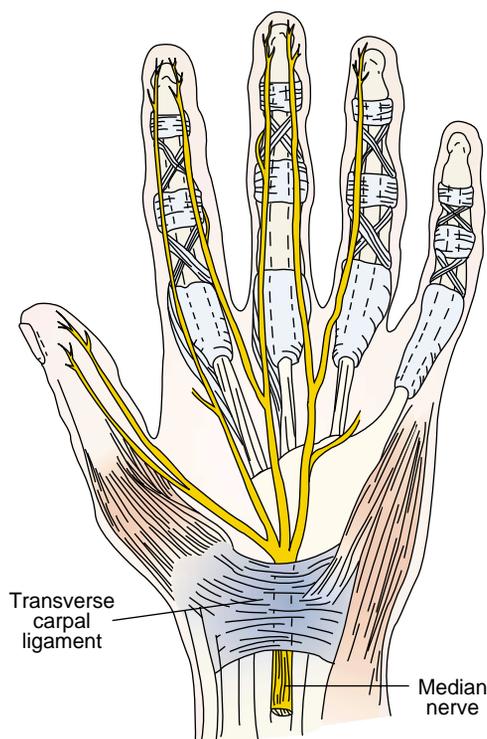
Median nerve

■ **FIGURE 38-11** ■ Carpal tunnel syndrome: compression of the median nerve by the transverse carpal ligament. (Courtesy Carole Russell Hilmer, C.M.I.)

Diagnosis usually is based on sensory disturbances confined to median nerve distribution. Electromyography and nerve conduction studies often are done to confirm the diagnosis and exclude other causes of the disorder.

Treatment includes avoidance of use, splinting, and anti-inflammatory medications. Measures to decrease the causative repetitive movements should be initiated. Splints may be confined to nighttime use. When splinting is ineffective, corticosteroids may be injected into the carpal tunnel to reduce inflammation and swelling. Surgical intervention consists of operative division of the volar carpal ligaments as a means of relieving pressure on the medial nerve.

Polyneuropathies. Polyneuropathies involve demyelination or axonal degeneration of multiple peripheral nerves that leads to symmetric sensory, motor, or mixed sensorimotor deficits. Typically, the longest axons are involved first, with symptoms beginning in the distal part of the extremities. If the autonomic nervous system is involved, there may be postural hypotension, constipation, and impotence. Polyneuropathies can result from immune mechanisms (*e.g.*, Guillain-Barré syndrome), toxic agents (*e.g.*, arsenic polyneuropathy, lead polyneuropathy, alcoholic polyneuropathy), and metabolic diseases (*e.g.*, diabetes mellitus, uremia). Different causes tend to affect axons of different diameters and to affect sensory, motor, or autonomic neurons to different degrees.

Guillain-Barré Syndrome. Guillain-Barré syndrome is an acute inflammatory polyneuropathy. The annual incidence of Guillain-Barré syndrome is approximately 1 case per 50,000 persons, and it is more common with increasing age.[13] Approximately 80% to 90% of persons with the disease achieve a spontaneous recovery.

The disorder involves an infiltration of mononuclear cells around the capillaries of the peripheral neurons, edema of the endoneurial compartment, and demyelination of ventral spinal roots. The cause of Guillain-Barré syndrome is unknown. Approximately two thirds of cases follow an infection that is seemingly mundane and often of viral origin.[6] There is an association with preceding gastrointestinal tract infection with *Campylobacter jejuni*.[14] A widely studied outbreak of the disorder followed the swine flu vaccination program of 1976 and 1977.[15] It has been suggested that an altered immune response to peripheral nerve antigens contributes to the development of the disorder.

The disorder is characterized by progressive ascending muscle weakness of the limbs, producing a symmetric flaccid paralysis. Symptoms of paresthesia and numbness often accompany the loss of motor function. The rate of disease progression varies, and there may be disproportionate involvement of the upper or lower extremities. Paralysis may progress to involve the respiratory muscles; approximately 20% of persons with the disorder require ventilatory assistance.[13] ANS involvement that causes postural hypotension, arrhythmias, facial flushing, abnormalities of sweating, and urinary retention is common.

Guillain-Barré syndrome usually presents as a medical emergency. There may be a rapid development of ventilatory failure and autonomic disturbances that threaten circulatory function. Treatment includes support of vital functions and prevention of complications such as skin breakdown and thrombophlebitis. Clinical trials have shown the effectiveness of plasma-

pheresis in decreasing morbidity and shortening the course of the disease. Treatment is most effective if initiated early in the course of the disease.

Back Pain and Intervertebral Disk Injury

Back Pain

Low back pain is an exceeding common health problem. The differential diagnosis is broad and includes muscle strain, primary spine disease (*e.g.*, disk herniation, degenerative arthritis [discussed in Chapter 43]), and systemic disease (*e.g.*, metastatic cancer). Although acute back problems commonly are attributed to a herniated intervertebral disk, most are caused by other, less serious conditions, such as muscle strain. It has been reported that 90% of persons with acute lower back problems of less than 3 months' duration experience spontaneous recovery.[16] The diagnostic challenge is to identify those persons who require more extensive evaluation for more serious problems, including disk herniation.[16]

Treatment of back pain usually is conservative and consists of analgesic medications and education on how to protect the back. Pain relief usually can be provided using nonsteroidal anti-inflammatory drugs, although short-term use of opioid pain medications may be required for severe pain. Muscle relaxants may be used on a short-term basis. Bed rest, once the mainstay of conservative therapy, is now understood to be ineffective for acute back pain.[17] Instruction in the correct mechanics for lifting and methods of protecting the back is important. Conditioning exercises of the trunk muscles, particularly the back extensors, may be recommended for persons with acute low back problems, particularly if the problem persists. Surgical treatment may be indicated when herniation is documented by some imaging procedure or in the presence of consistent pain or consistent neurologic deficit that has failed to respond to conservative therapy.

Herniated Intervertebral Disk

The intervertebral disk is considered the most critical component of the load-bearing structures of the spinal column. The intervertebral disk consists of a soft, gelatinous center called the *nucleus pulposus,* which is encircled by a strong, ringlike collar of fibrocartilage called the *annulus fibrosus.* The structural components of the disk make it capable of absorbing shock and changing shape while allowing movement. With dysfunction, the nucleus pulposus can be squeezed out of place and herniate through the annulus fibrosus, a condition referred to as a *herniated* or *slipped disk* (Fig. 38-12A and B).

The intervertebral disk can become dysfunctional because of trauma, the effects of aging, or degenerative disorders of the spine. Trauma accounts for 50% of disk herniations. It results from activities such as lifting while in the flexed position, slipping, falling on the buttocks or back, or suppressing a sneeze. With aging, the gelatinous center of the disk dries out and loses much of its elasticity, causing it to fray and tear. Degenerative
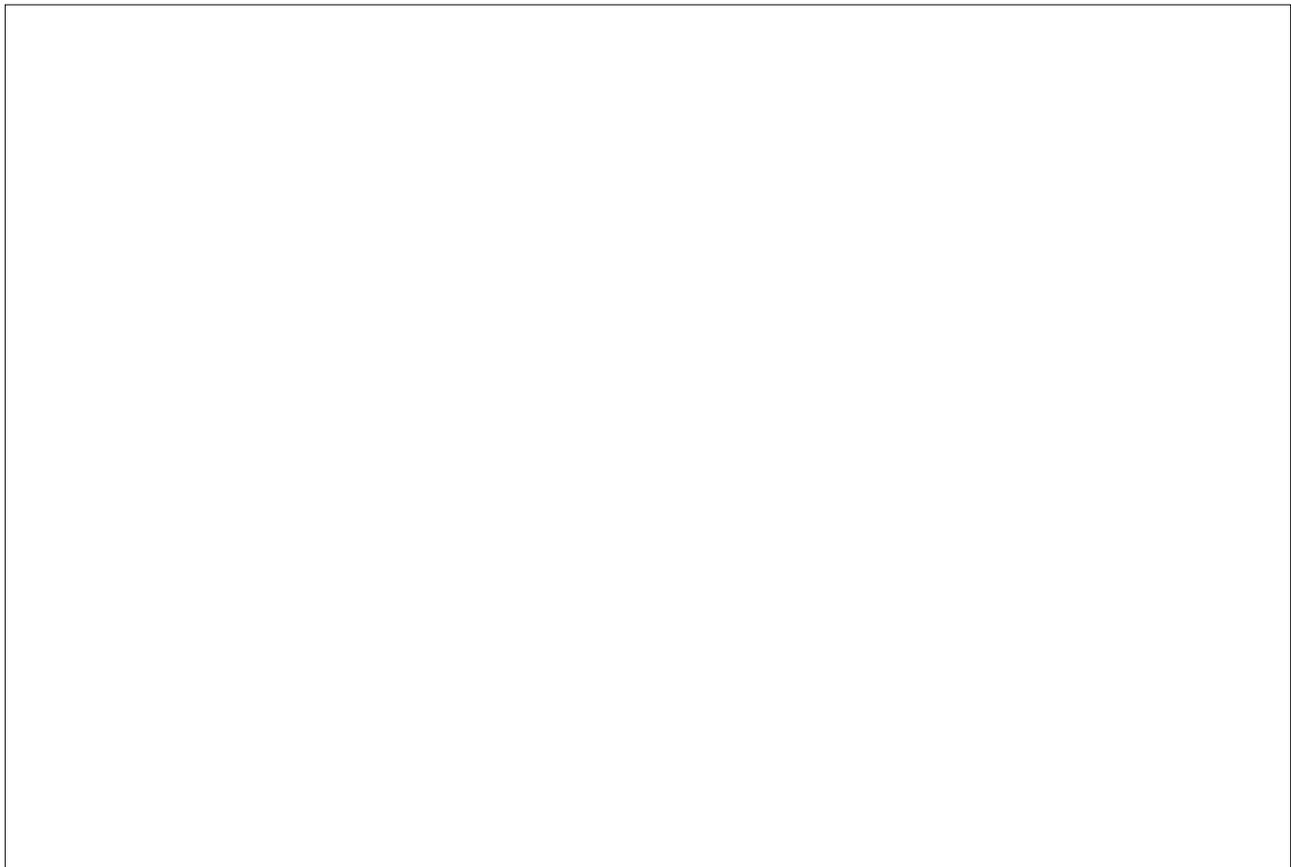
■ **FIGURE 38-12** ■ Herniated intervertebral disk (**A**) longitudinal section. (**B**) Cross-section. (**C**) location of L4-5 and S1-5 spinal nerves with site of L4/5 herniation of nucleus pulposus indicated.

processes such as osteoarthritis or ankylosing spondylitis predispose to malalignment of the vertebral column.

The cervical and lumbar regions are the most flexible area of the spine and are most often involved in disk herniations. Usually, herniation occurs at the lower levels of the lumbar spine, where the mass being supported and the bending of the vertebral column are greatest. Approximately 90% to 95% of lumbar herniations occur in the L4 or L5 to S1 regions. With herniations of the cervical spine, the most frequently involved levels are C6 to C7 and C5 to C6.[5] Protrusion of the nucleus pulposus usually occurs posteriorly and toward the intervertebral foramen and its contained spinal nerve root, where the anulus fibrosus is relatively thin and poorly supported by either the posterior or anterior ligaments[18] (see Fig. 38-12A).

The level at which a herniated disk occurs is important (Fig. 38-12C). When the injury occurs in the lumbar area, only the cauda equina is irritated or crushed. Because these elongated dorsal and ventral roots contain endoneurial tubes of connective tissue, regeneration of the nerve fibers is likely. However, several weeks or months are required for full recovery to occur because of the distance to the innervated muscle or skin of the lower limbs.

The signs and symptoms of a herniated disk are localized to the area of the body innervated by the nerve roots and include both motor and sensory manifestations (Fig. 38-13). Pain is the first and most common symptom of a herniated disk. The nerve roots of L4, L5, S1, S2, and S3 give rise to a syndrome of back pain that spreads down the back of the leg and over the sole of the foot. The pain is usually intensified with coughing, sneezing, straining, stooping, standing, and the jarring motions that occur during walking or riding. Slight motor weakness may occur, although major weakness is rare. The most common sensory deficits from spinal nerve root compression are paresthesias and numbness, particularly of the leg and foot. Knee and ankle reflexes also may be diminished or absent.

A herniated disk must be differentiated from other causes such as traumatic injury or fracture of the vertebral column, tumor, infection, cauda equina syndrome (see spinal cord injury), or other conditions that cause back pain.[16] Diagnostic measures include history and physical examination. Neurologic assessment includes testing of muscle strength and reflexes. Other diagnostic methods include radiographs of the back, magnetic resonance imaging (MRI), myelography, and computed tomography (CT).[19] Myelography, MRI, and CT usually are reserved for persons suspected of having more complex causes of back pain.

In summary, disorders of motor function include disorders of the skeletal muscle, the neuromuscular junction, and the peripheral nerves. *Muscular dystrophy* is a term used to describe a number of disorders that produce progressive deterioration of skeletal muscle. Muscle necrosis is followed by fat and connective tissue replacement. One form, Duchenne muscular dystrophy, is inherited as a X-linked trait and transmitted by the mother to her male offspring.

Myasthenia gravis is a disorder of the neuromuscular junction resulting from a deficiency of functional acetylcholine receptors, which causes weakness of the skeletal muscles. Because the disease affects the neuromuscular junction, there is no loss of sensory function. The most common manifestations are weakness of the eye muscles, with ptosis and diplopia; the jaw muscles, which make chewing and swallowing difficult; and proximal muscles and extremities, which make climbing stairs and lifting objects difficult.

Disorders of peripheral nerves include mononeuropathies and polyneuropathies. Mononeuropathies involve a single spinal nerve, plexus, or peripheral nerve trunk. Carpal tunnel syndrome, a mononeuropathy, is caused by compression of the medial nerve that passes through the carpal tunnel in the wrist. Polyneuropathies involve multiple peripheral nerves and produce symmetric sensory, motor, and mixed sensorimotor deficits. Guillain-Barré syndrome is a subacute polyneuropathy of uncertain origin. It causes progressive ascending motor, sensory, and ANS manifestations. Respiratory involvement may occur and necessitate mechanical ventilation.

Acute back pain is most commonly the result of conditions such as muscle strain, with treatment that focuses on measures to improve activity tolerance. A herniated intervertebral disk is characterized by protrusion of the nucleus pulposus into the spinal canal with irritation or compression of the nerve root. Usually, herniation occurs at the lower levels of the lumbar and sacral (L4 or L5 to S1) and cervical (C6 to C7 and C5 to C6) regions of the spine. The signs and symptoms of a herniated disk are localized to the area of the body innervated by the nerve roots and include pain and both motor and sensory manifestations.

Nerve root	L4	L5	S1
Pain			
Numbness			
Motor weakness	Extension of quadriceps	Dorsiflexion of great toe and foot	Plantar flexion of great toe and foot

■ **FIGURE 38-13** ■ Dermatomes of the leg (L1 through S5) where pain and numbness would be experienced with spinal root irritation.

BASAL GANGLIA AND CEREBELLUM DISORDERS

The Basal Ganglia

The basal ganglia are a group of deep, interrelated subcortical nuclei that play an essential role in control of movement. They receive indirect input from the cerebellum and from all sensory ganglia systems, including vision, and the motor cortex. The structural components of the basal ganglia include the caudate nucleus, putamen, and the globus pallidus in the forebrain. The caudate and putamen are collectively referred to as the *neostriatum*, and the putamen and the globus pallidus form a wedge-shaped region called the *lentiform nucleus*. Two other structures, the *subthalamic nucleus* of the diencephalon and the *substantia nigra* of the midbrain, are considered part of the basal ganglia (Fig. 38-14). The substantia nigra contains cells that use dopamine as a neurotransmitter and are rich in a black pigment called *melanin*. The high concentration of melanin gives the structure a black color, thus the name *substantia nigra*. The axons of the substantia nigra form the *nigrostriatal pathway*, which supplies dopamine to the striatum. The dopamine released from the substantia nigra regulates the overall excitability of the striatum and release of other neurotransmitters.

The basal ganglia have input structures that receive afferent information from outside structures, internal circuits that connect the various structures of the basal ganglia, and output structures that deliver information to other brain centers. The neostriatum represents the major input structure for the basal ganglia. Information coming from virtually all areas of the cortex and thalamus are projected to the neostriatum. The output areas of the basal ganglia have both ascending and descending components. The major ascending output is transmitted to thalamic nuclei, which process all incoming sensory information that is transmitted to the cerebral cortex. Descending output is directed to the midbrain, brain stem, and spinal cord. The output functions of the basal ganglia are mainly inhibitory.

The most is known about the inhibitory basal ganglia loop involved in modulating cortical motor control. This loop regulates release of stereotyped movement patterns that add efficiency and gracefulness to precise and delicate cortically controlled movements. These movements include inherited patterns that add efficiency, balance, and gracefulness to motion, such as the swinging of the arms during walking and running, and the highly learned automatic postural and follow-through movements of throwing a ball or swinging a bat.

An additional modulating circuit involves a neostriatal inhibitory projection on the substantia nigra. The substantia nigra projects dopaminergic axons back on the neostriatum. A deficiency in the dopaminergic projection of this modulating circuit is implicated in Parkinson's syndrome. The function of the neostriatum also involves local cholinergic interneurons, and their destruction is thought to be related to the choreiform movements of Huntington's chorea, another basal ganglia-related syndrome (see Chapter 37).

Movement Disorders

Disorders of the basal ganglia comprise a complex group of motor disturbances characterized by involuntary movements, alterations in muscle tone, and disturbances in body posture. Unlike disorders of the motor cortex and corticospinal tract, lesions of the basal ganglia disrupt movement but do not cause paralysis.

Movement disorders associated with dysfunction of the basal ganglia include bradykinesis, hyperkinesis, and abnormal movements. Hyperfunction of the basal ganglia inhibitory loop result in excessive inhibition of cortical function, resulting in *bradykinesia* or *hypokinesis*. Reduced function of the basal ganglia loop results in *hyperkinesis*, or release of movement patterns at inappropriate times or sometimes continuously. Pathologically released patterns that often are disabling include rigidity and movement disorders. These movement patterns are not under cortical control and often are referred to as *involuntary movements*.

Involuntary movements include tremor, tics, choreiform movements, athetoid movements, and ballismus. These disorders are summarized in Table 38-1. Tremor is caused by involuntary, oscillating contractions of opposing muscle groups around a joint. It usually is fairly uniform in frequency and amplitude. Certain tremors are considered physiologic in that they are transitory and normally occur under conditions of increased muscle tone, as in highly emotional situations, or they may be related to muscle fatigue or reduced body temperature (*i.e.*, shivering). Toxic tremors are produced by hyperexcitability related to conditions such as thyrotoxicosis. The tremor of Parkinson's disease is caused by degenerative changes in the basal ganglia. Tics involve sudden and irregularly occurring contractions of whole muscles or major portions of a muscle. These are particularly evident in the muscles of the face but can occur elsewhere.

Choreiform movements are sudden, jerky, and irregular but are coordinated and graceful. They can involve the distal limb, face, tongue, or swallowing muscles. Choreiform movements, such as those seen in Huntington's disease (see Chapter 40), are accentuated by movement and by environmental stimulation; they often interfere with normal movement patterns. The word *chorea* originated from the Greek word meaning "to dance." There may be grimacing movements of the face; raising of the eyebrows; rolling of the eyes; and curling, protrusion, and withdrawal of the tongue. In the limbs, the movements largely are distal; there may movements that mimic piano playing with alternating extension and flexion of the fingers. The shoulders may be elevated and depressed or rotated. Movements
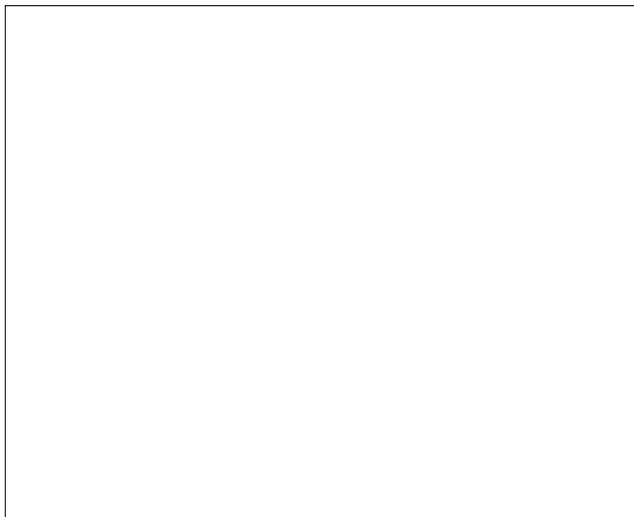
■ **FIGURE 38-14** ■ Basal ganglia.

TABLE 38-1	Involuntary Movements Disorders Associated With Extrapyramidal Disorders

Movement Disorder	Characteristics
Tremor	Rhythmic oscillating contractions or movements of whole muscles or major portions of a muscle. They can occur as resting tremors, which are prominent at rest and decrease or disappear with movement; intention tremors, which increase with activity and become worse when the target is reached; and postural tremors, which appear when the affected part is maintained in a stabilized position.
Tics	Irregularly occurring brief, repetitive, stereotyped, coordinated movements such as winking, grimacing, or shoulder shrugging
Chorea	Brief, rapid, jerky, and irregular movements that are coordinated and graceful. The face, head, and distal limbs are most commonly involved. They often interfere with normal movement patterns.
Athetosis	Continuous, slow, wormlike, twisting and turning motions of a limb or body that most commonly involve the face and distal extremities and are often associated with spasticity
Ballismus	Involve violent sweeping, flinging-type limb movements, especially on one side of the body (hemiballismus)
Dystonia	Abnormal maintenance of posture results from a twisting, turning motion of the limbs, neck, or trunk. Motions are similar to athetosis but involve larger portions of the body. They can result in grotesque and twisted postures.
Dyskinesias	Rhythmic, repetitive, bizarre movements that chiefly involve the face, mouth, jaw, or tongue, causing grimacing, pursing of the lips, protrusion of the tongue, opening and closing of the mouth, and deviations of the jaw. The limbs are affected less often.

(From Bates B. [1991]. *A guide to physical examination and history taking* [5th ed., pp. 554–556]. Philadelphia: J.B. Lippincott)

of the face or limbs may occur alone or, more commonly, in combination.

Athetoid movements are relatively continuous, wormlike twisting and turning motions of the joints of a limb or body, such as those seen in one form of cerebral palsy. These result from continuous and prolonged contraction of agonist and antagonistic muscle groups. The term *ballismus* originated from a Greek word meaning "to jump around." Ballistic movements are violent, sweeping, flinging motions, especially of the limbs on one side of the body (hemiballismus). They may occur as the result of a small stroke involving the subthalamic nucleus on the opposite side of the brain.

Dystonia refers to the abnormal maintenance of a posture resulting from a twisting, turning movement of the limbs, neck, or trunk. These postures often result from simultaneous contraction of agonist and antagonist muscles. Long-sustained simultaneous hypertonia across a joint can result in degenerative changes and permanent fixation in unusual postures. These effects can occur as a side effect of some antipsychotic medications. *Spasmodic torticollis*, the most common type of dystonia, affects the muscles of the neck and shoulder. The condition, which is caused by bilateral and simultaneous contraction of the neck and shoulder muscles, results in unilateral head turning or head extension, sometimes limiting rotation. Elevations of the shoulder commonly accompany the spasmodic movements of the head and neck. Immobility of the cervical vertebrae eventually can lead to degenerative fixation in the twisted posture. Torsional spasm involving the trunk also can occur.

Dyskinesias are rhythmic, repetitive, bizarre movements. They frequently involve the face, mouth, jaw, and tongue, causing grimacing, pursing of the lips, or protrusion of the tongue. The limbs are affected less often. Tardive dyskinesia is an untoward reaction that can develop with long-term use of some of the antipsychotic medications.

Parkinson's Disease

Parkinson's disease is a degenerative disorder of basal ganglia function that results in variable combinations of tremor, rigidity, and bradykinesia. The disorder is characterized by progressive destruction of the nigrostriatal pathway, with subsequent reduction in striatal concentrations of dopamine. As many as 1.5 million people in the United States are affected by the disease.[20] It usually begins after 50 years of age; most cases are diagnosed in the sixth and seventh decade of life.

The clinical syndrome arising from the degenerative changes in basal ganglia function often is referred to as *parkinsonism*. Parkinson's disease, the most common form of parkinsonism, is named after James Parkinson, a British physician who first described the disease in a paper he published in 1817 on the "shaking palsy."[21] In Parkinson's disease, also known as idiopathic parkinsonism, dopamine depletion results from degeneration of the dopamine nigrostriatal system. Parkinsonism can also develop as a postencephalitic syndrome, as a side effect of therapy with antipsychotic drugs that block dopamine receptors, as a toxic reaction to a chemical agent, or as an outcome of severe carbon monoxide poisoning. Symptoms of parkinsonism also may accompany conditions such as cerebral vascular disease, brain tumors, repeated head trauma, or degenerative neurologic diseases that structurally damage the nigrostriatal pathway.

Drug-induced parkinsonism can follow the administration of antipsychotic drugs in high doses (*e.g.*, phenothiazines, butyrophenones). These drugs block dopamine receptors and dopamine output by the cells of the substantia nigra. Of interest in terms of research was the development of Parkinson's disease in several persons who had attempted to make a narcotic drug and instead synthesized a compound called MPTP (1-methyl-phenyl-2,3,6-tetrahydropyridine).[22] This compound selectively destroys the dopaminergic neurons of the substantia nigra. This incident prompted investigations into the

role of toxins that are produced by the body as a part of metabolic processes and those that enter the body from outside sources in the pathogenesis of Parkinson's disease. One theory is that the auto-oxidation of catecholamines such as dopamine during melanin synthesis has the potential for injuring neurons in the substantia nigra. Accordingly, the development of Parkinson's disease may be related to oxidative metabolites of this process and the inability of neurons to render these products harmless. MPTP is an inhibitor of the metabolic pathway that functions in the inactivation of these metabolites, suggesting that it may produce Parkinson's disease in a manner similar to the naturally occurring disease.[6]

A recent discovery suggests that genetic susceptibility may play a role in the pathogenesis of early-onset (before 45 years of age) Parkinson's disease. A mutation in a gene called the *Parkin gene* has been identified in a high percentage of family members and persons with early-onset Parkinson's disease.[23]

Clinical Course. The cardinal manifestations of Parkinson's disease are tremor, rigidity, and bradykinesia or slowness of movement.[24] Other advanced-stage parkinsonian manifestations are falls, fluctuations in motor function, neuropsychiatric disorders, and sleep disorders.

Tremor is the most visible manifestation of the disorder. The tremor affects the distal segments of the limbs, mainly the hands and feet; head, neck, face, lips, and tongue; or jaw. It is characterized by rhythmic, alternating flexion and contraction movements (four to six beats per minute) that resemble the motion of rolling a pill between the thumb and forefinger. The tremor usually is unilateral, occurs when the limb is supported and at rest, and disappears with movement and sleep. The tremor eventually progresses to involve both sides of the body. Although the most noticeable sign of Parkinson's disease, tremor usually is the least disabling because of the dampening effect of purposeful movement.

Rigidity is defined as resistance to movement of both flexors and extensors throughout the full range of motion. It is most evident during passive joint movement and involves jerky, cogwheel-type or ratchet-like movements that require considerable energy to perform. Flexion contractions may develop as a result of the rigidity. As with tremor, rigidity usually begins unilaterally but progresses to involve both sides of the body.

Bradykinesia is characterized by slowness in initiating and performing movements and difficulty in sudden, unexpected stopping of voluntary movements. Unconscious associative movements occur in a series of disconnected steps, rather than in a smooth, coordinated manner. This is the most disabling of the symptoms of Parkinson's disease. Persons with Parkinson's disease have difficulty initiating walking and difficulty turning. While walking, they may freeze in place and feel as if their feet are glued to the floor, especially when moving through a doorway or preparing to turn. When they walk, they lean forward to maintain their center of gravity and take small, shuffling steps without swinging their arms, and they have difficulty in changing their stride (Fig. 38-15). Loss of postural reflexes predisposes them to falling, often backward. Emotional and voluntary facial movements become limited and slow as the disease progresses, and facial expression becomes stiff and masklike. There is loss of the blinking reflex and a failure to express emotion. The tongue, palate, and throat muscles become
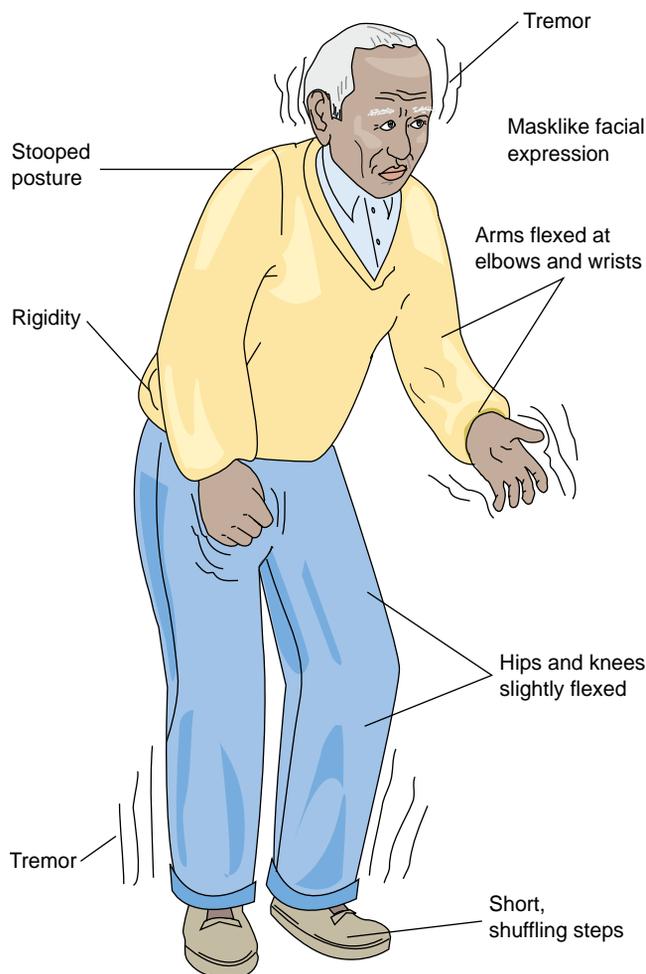

■ FIGURE 38-15 ■ The clinical features of Parkinson's disease.

rigid; the person may drool because of difficulty in moving the saliva to the back of the mouth and swallowing it. The speech becomes slow and monotonous, without modulation and poorly articulated.

Because the basal ganglia also influence the ANS, persons with Parkinson's disease often have excessive and uncontrolled sweating, sebaceous gland secretion, and salivation. Autonomic symptoms such as lacrimation, dysphagia, orthostatic hypotension, thermal regulation, constipation, impotence, and urinary incontinence may be present, especially late in the disease.

Dementia is an important feature associated with Parkinson's disease. It occurs in approximately 20% of persons with the disease and develops late in the course of the disease.[24] The mental state of some persons with Parkinson's disease may be indistinguishable from that seen in Alzheimer's disease. It has been suggested that many of the brain changes in both diseases may result from degeneration of acetylcholine-containing neurons.

Treatment. The approach to treatment of Parkinson's disease must be highly individualized. It includes nonpharmacologic, pharmacologic, and when indicated, surgical methods. Nonpharmacologic interventions offer group support, education,

daily exercise, and adequate nutrition. Botulism toxin injections may be used in the treatment of dystonias such as eyelid spasm and limb dystonias that frequently are associated with Parkinson's disease.[25]

Pharmacologic treatment usually is determined by the severity of symptoms. Antiparkinson drugs act by increasing the functional ability of the underactive dopaminergic system, or they reduce the excessive influence of excitatory cholinergic neurons. They include drugs that increase dopamine levels (*e.g.*, levodopa), augment the release of dopamine (*e.g.*, amantadine), function as dopamine agonists or directly stimulate dopamine receptors (*e.g.*, bromocriptine, pergolide, pramipexole, ropinirole), or inhibit the metabolic breakdown of dopamine (*e.g.*, selegiline). Because dopamine transmission is disrupted in Parkinson's disease, there is a preponderance of cholinergic activity, which may be treated with anticholinergic drugs.

Surgical treatment includes thalamotomy or pallidectomy performed using stereotactic surgery. With these procedures, part of the thalamus or globus pallidum in the basal ganglia is destroyed using an electrical stimulator or supercooled tip of a metal probe (cryothalamotomy). Brain mapping is done during the surgery to identify and prevent injury to sensory and motor tracts. Surgery is generally confined to one side of the brain and is usually restricted to persons who have not experienced satisfactory response to drug therapy.

The Cerebellum

The cerebellum, or "little brain," constitutes only 10% of the total volume of the brain but contains more than half of all its neurons.[1] The cerebellum is responsible for smoothing the temporal and spatial aspects of rapid movement anywhere in the body. It does this by evaluating disparities between intention and action and by adjusting the operation of motor centers in the cortex while the movement is in progress as well as during repetitions of the same movement. The cerebellum also appears to have a role in learning both motor and cognitive tasks in which skilled responses are developed through repeated practice. It does not alter sensory thresholds or the strength of muscle contraction.

The cerebellum is located in the posterior fossa of the cranium superior to the pons (see Chapter 36, Fig. 36–19). It is separated from the cerebral hemispheres by a fold of dura mater, the tentorium cerebelli. The cerebellum consists of a small, unpaired median portion, called the *vermis*, and two large lateral masses, the *cerebellar hemispheres*. In contrast to the brain stem with its external white matter and internal gray nuclei, the cerebellum, like the cerebrum, has an outer cortex of gray matter overlying the white matter. Several masses of gray matter, called the *deep cerebellar nuclei*, border the roof of the fourth ventricle. Cells of the cerebellar cortex and the deep nuclei interact and axons from the latter send information to many regions, particularly to the motor cortex by means of a thalamic relay.

Synergistic (*i.e.*, temporal and spatial smoothing) functions of the cerebellum participate in all movements of limbs, trunk, head, larynx, and eyes, whether the movement is part of a voluntary movement or of a highly learned semiautomatic or automatic movement. During highly skilled movements, the motor cortex sends signals to the cerebellum, informing it about the movement that is to be performed. The cerebellum makes continuous adjustments, resulting in smoothness of movement, particularly during delicate maneuvers. Highly skillful movement requires extensive motor training, and considerable evidence suggests many of these learned movement patterns involve cerebellar circuits.

The cerebellum receives proprioceptor input from the vestibular system; feedback from the muscles, tendons, and joints; and indirect signals from the somesthetic, visual, and auditory systems that provide background information for ongoing movement. Sensory and motor information from a given area of the body is sent to the same area in the cerebellum. In this way, the cerebellum can assess continuously the status of each body part—position, rate of movement, and forces such as gravity that are opposing movement. The cerebellum compares what is actually happening with what is intended to happen. It then transmits the appropriate corrective signals back to the motor system, instructing it to increase or decrease the activity of the participating muscle groups so that smooth and accurate movements can be performed.

Cerebellar Dysfunction

Cerebellar dysfunction can be caused by injuries, global ischemia, occlusion of any of the cerebellar arteries, cerebral hemorrhage, and neoplastic lesions. Massive cerebellar infarction may lead to coma, tonsillar herniation, and death. Chronic alcoholism can lead to atrophy of the superior vermis of the cerebellulum.[7]

The signs of cerebellar dysfunction can be grouped into three classes: (1) vestibulocerebellar disorders, (2) cerebellar ataxia or decomposition of movement, and (3) cerebellar tremor. These disorders occur on the side of cerebellar damage. The abnormality of movement occurs whether the eyes are open or closed. Visual monitoring of movement cannot compensate for cerebellar defects.

Damage to the part of the cerebellum associated with the vestibular system leads to difficulty or inability to maintain a steady posture of the trunk, which normally requires constant readjusting movements. This is seen as an unsteadiness of the trunk, called *truncal ataxia*, and it can be so severe that standing is not possible. The ability to fix the eyes on a target also can be affected. Constant conjugate readjustment of eye position, called *nystagmus*, results and makes reading extremely difficult, especially when the eyes are deviated toward the side of cerebellar damage.

Cerebellar ataxia and tremor are different aspects of defects in the smooth, continuously correcting functions. Cerebellar dystaxia or, if severe, ataxia includes a decomposition of movement; each succeeding component of a complex movement occurs separately instead of being blended into a smoothly proceeding action. Because ethanol specifically affects cerebellar function, persons who are inebriated often walk with a staggering and unsteady gait. Rapid alternating movements such as supination-pronation-supination of the hands are jerky and performed slowly (dysdiadochokinesia). Reaching to touch a target breaks down into small sequential components, each going too far, followed by overcorrection. The finger moves jerkily toward the target, misses, corrects in the other direction, and misses again, until the target is finally reached. This is

called *over-and-under reaching.* Tests of cerebellar function (walking a straight line and touching the nose with the index finger) are often used; these are the same tests used by law enforcement officials for screening persons suspected of driving while intoxicated.

Cerebellar tremor is a rhythmic back-and-forth movement of a finger or toe that worsens as the target is approached. The tremor results from the inability of the damaged cerebellar system to maintain ongoing fixation of a body part and to make smooth, continuous corrections in the trajectory of the movement; overcorrection occurs, first in one direction and then the other. Often, the tremor of an arm or leg can be detected during the beginning of an intended movement. The common term for cerebellar tremor is *intention tremor.* Cerebellar function as it relates to tremor can be assessed by asking a person to touch one heel to the opposite knee, to gently move the toes along the back of the opposite shin, or to move the hand so as to touch the nose with a finger.

Cerebellar function also can affect the motor skills of chewing and swallowing (dysphagia) and of speech (dysarthria). Normal speech requires smooth control of respiratory muscles and highly coordinated control of the laryngeal, lip, and tongue muscles. Cerebellar dysarthria is characterized by slow, slurred speech of continuously varying loudness. Rehabilitative efforts directed by speech therapists include learning to slow the rate of speech and to compensate as much as possible through the use of less-affected muscles.

> **In summary,** alterations in coordination of muscle movements and abnormal muscle movements result from disorders of the basal ganglia and cerebellum. The basal ganglia organize basic movement patterns into more complex patterns and release them when commanded by the motor cortex, contributing gracefulness to cortically initiated and controlled skilled movements. Disorders of the basal ganglia are characterized by involuntary movements, alterations in muscle tone, and disturbances in posture. These disorders include tremor, tics, hemiballismus, chorea, athetosis, dystonias, and dyskinesias.
>
> Parkinsonism, a disorder of the basal ganglia, is characterized by destruction of the nigrostriatal pathway, with a subsequent reduction in striatal concentrations of dopamine. This results in an imbalance between the inhibitory effects of dopaminergic basal ganglia functions and an increase in the excitatory cholinergic functions. The disorder is manifested by combinations of slowness of movement (*i.e.*, bradykinesia), increased muscle tonus and rigidity, rest tremor, gait disturbances, and impaired autonomic postural responses.
>
> The cerebellum is responsible for smoothing the temporal and spatial aspects of rapid movement anywhere in the body. It does this by evaluating disparities between intention and action and by adjusting the operation of motor centers in the cortex while the movement is in progress as well as during repetitions of the same movement. The cerebellum also appears to have a role in learning both motor and cognitive tasks in which skilled responses are developed through repeated practice. Cerebellar disorders include vestibulocerebellar dysfunction, cerebellar ataxia, and cerebellar tremor.

SHORT

UPPER AND LOWER MOTONEURON DISORDERS

Upper and Lower motoneurons innervate the skeletal muscles and are essential for motor function. The UMNs are fully contained within the CNS. They include the motor neurons arising in the motor areas of the cortex and their fibers as they project through the brain and descend in the spinal cord. Disorders that affect UMNs include multiple sclerosis and spinal cord injury (discussed later). Stroke, which is a common cause of UMN damage, is discussed in Chapter 37. Amyotrophic lateral sclerosis is a mixed UMN and LMN disorder.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also known as *Lou Gehrig's disease* after the famous New York Yankees baseball player, is a devastating neurologic disorder that selectively affects motor function. ALS is primarily a disorder of middle to late adulthood, affecting persons between 55 and 60 years of age, with men developing the disease nearly twice as often as women. The disease typically follows a progressive course, with a mean survival period of 2 to 5 years from the onset of symptoms.

ALS affects motoneurons in three locations: the anterior horn cells of the spinal cord; the motor nuclei of the brain stem, particularly the hypoglossal nuclei; and the UMNs of the cerebral cortex.[26] The fact that the disease is more extensive in the distal, rather than the proximal, parts of the affected tracts in the lower spinal cord suggests that affected neurons first undergo degeneration at their distal terminals and that the disease proceeds in a centripetal direction until ultimately the parent nerve cell dies. A remarkable feature of the disease is that the entire sensory system, the regulatory mechanisms of control and coordination of movement, and the intellect remain intact. The neurons for eye movement and the parasympathetic neurons in the sacral spinal cord also are spared.

Degeneration and loss of neurons in the primary motor cortex leads to loss of fibers within the corticospinal tract and lateral and anterior columns of the spinal cord.[6] It is this fiber atrophy, called *amyotrophy,* that appears in the name of the disease. The loss of nerve fibers in lateral columns of the white matter of the spinal cord along with fibrillary gliosis imparts a firmness or sclerosis to this CNS tissue; the term *lateral sclerosis* designates these changes.

The cause of LMN and UMN destruction in ALS is uncertain. Five percent to 10% of cases are familial; the others are believed to be sporadic, with no family history of the disease. Recently, mutations to a gene encoding superoxide dismutase 1 (SOD1) was mapped to chromosome 21. This enzyme functions in the prevention of free radical formation (see Chapter 2). The mutation accounts for 20% of familial ALS, with the remaining 80% being caused by mutations in other genes.[26] Five percent of persons with sporadic ALS also have SOD1 mutations. Possible targets of SOD1-induced toxicity include the neurofilament proteins, which function in the axonal transport of molecules necessary for the maintenance of axons.[26] Another suggested mechanism of pathogenesis in ALS is exotoxic injury through activation of glutamate-gated ion channels, which are distinguished by their sensitivity to *N*-methyl-D-aspartic acid

(see Chapter 37). The possibility of glutamate excitotoxicity in the pathogenesis of ALS was suggested by the finding of increased glutamine levels in the cerebrospinal fluid of patients with sporadic ALS.[26] Although autoimmunity has been suggested as a cause of ALS, the disease does not respond to the immunosuppressant agents that normally are used in treatment of autoimmune disorders.

Clinical Course

The symptoms of ALS may be referable to UMN or LMN involvement. Manifestations of UMN lesions include weakness, spasticity or stiffness, and impaired fine motor control.[26,27] Dysphagia (difficulty swallowing), dysarthria (impaired articulation of speech), and dysphonia (difficulty making the sounds of speech) may result from brain stem LMN involvement or from dysfunction of UMNs descending to the brain stem. Manifestations of LMN destruction include fasciculations, weakness, muscle atrophy, and hyporeflexia. Muscle cramping involving the distal legs often is an early symptom. The most common clinical presentation is slowly progressive weakness and atrophy in distal muscles of one upper extremity. This is followed by regional spread of clinical weakness, reflecting involvement of neighboring areas of the spinal cord. Eventually, UMNs and LMNs involving multiple limbs and the head are affected. In the more advanced stages, muscles of the palate, pharynx, tongue, neck, and shoulders become involved, causing impairment of chewing, swallowing, and speech. Dysphagia with recurrent aspiration and weakness of the respiratory muscles produces the most significant acute complications of the disease. Death usually results from involvement of cranial nerves and respiratory musculature.

Currently, there is no cure for ALS. Rehabilitation measures assist persons with the disorder to manage their disability, and respiratory and nutritional support allows persons with the disorder to survive longer than would otherwise have been the case. An antiglutamate drug, riluzole, is the only drug approved by the U.S. Food and Drug Administration (FDA) for treatment of ALS. The drug is designed to decrease glutamate accumulation and slow the progression of the disease.[26]

Multiple Sclerosis

Multiple sclerosis (MS), a demyelinating disease of the CNS, is a major cause of neurologic disability among young and middle-aged adults. Approximately two thirds of persons with MS experience their first symptoms between 20 and 40 years of age. In approximately 80% of the cases, the disease is characterized by exacerbations and remissions over many years in several different sites in the CNS.[28] Initially, there is normal or near-normal neurologic function between exacerbations. As the disease progresses, there is less improvement between exacerbations and increasing neurologic dysfunction.

The prevalence of MS varies considerably around the world. The disease is more prevalent in the colder northern latitudes; it is more common in the northern Atlantic states, the Great Lakes region, and the Pacific Northwest than in the southern parts of the United States. Other high-incidence areas include northern Europe, Great Britain, southern Australia, and New Zealand.[29] The incidence among women is almost double that of men. Although MS is not directly inherited, there is a familial predisposition in some cases, suggesting a genetic influence

on susceptibility. For example, there is evidence of a genetic linkage of MS susceptibility to the inherited major histocompatibility complex DR2 haplotype (Chapter 8).[6,28]

The pathophysiology of MS involves the demyelination of nerve fibers in the white matter of the brain, spinal cord, and optic nerve. In the CNS, myelin is formed by the oligodendrocytes, chiefly those lying among the nerve fibers in the white matter. The properties of the myelin sheath—high electrical resistance and low capacitance—permit it to function as an electrical insulator. Demyelinated nerve fibers display a variety of conduction abnormalities, ranging from decreased conduction velocity to conduction blocks.

The lesions of MS consist of hard, sharp-edged demyelinated or sclerotic patches that are macroscopically visible throughout the white matter of the CNS[7] (Fig. 38-16). These lesions, which represent the end result of acute myelin breakdown, are called *plaques*. The lesions have a predilection for the optic nerves, periventricular white matter, brain stem, cerebellum, and spinal cord white matter.[28] In an active plaque, there is evidence of ongoing myelin breakdown. The sequence of myelin breakdown is not well understood, although it is known that the lesions contain small amounts of myelin basic proteins and increased amounts of proteolytic enzymes, macrophages, lymphocytes, and plasma cells. Oligodendrocytes are decreased in number and may be absent, especially in older lesions. Acute, subacute, and chronic lesions often are seen at multiple sites throughout the CNS.

The lesions of MS are generally thought to result from an immune-mediated inflammatory response that occurs in genetically susceptible individuals. The demyelination process in MS is marked by prominent lymphocytic invasion in the lesion. The infiltrate in plaques contains both CD8+ and CD4+ T cells as well as macrophages. Both macrophages and cytotoxic CD8+ T cells are thought to induce oligodendrocyte injury. There also is evidence of antibody-mediated damage involving myelin oligodendroglial protein.[6] Magnetic resonance imaging has shown that the lesions of MS may occur in two stages: a first stage that involves the sequential development of small inflammatory lesions, and a second stage during which the lesions extend and consolidate and when demyelination and gliosis (scar formation) occur. It is not known whether the inflammatory process, present during the first stage, is directed against the myelin or against the oligodendrocytes that produce myelin. There is evidence that remyelination can occur in the CNS if the process that initiated the demyelination is halted before the oligodendrocyte dies.[28]

Clinical Course

The interruption of neural conduction in the demyelinated nerves is manifested by a variety of symptoms, depending on the location and extent of the lesion. Areas commonly affected by MS are the optic nerve (visual field), corticobulbar tracts (speech and swallowing), corticospinal tracts (muscle strength), cerebellar tracts (gait and coordination), spinocerebellar tracts (balance), medial longitudinal fasciculus (conjugate gaze function of the extraocular eye muscles), and posterior cell columns of the spinal cord (position and vibratory sensation). Typically, an otherwise healthy person presents with an acute or subacute episode of paresthesias, optic neuritis (*i.e.*, visual clouding or loss of vision in part of the visual field with pain on movement of the globe), diplopia, or specific types of gaze paralysis.
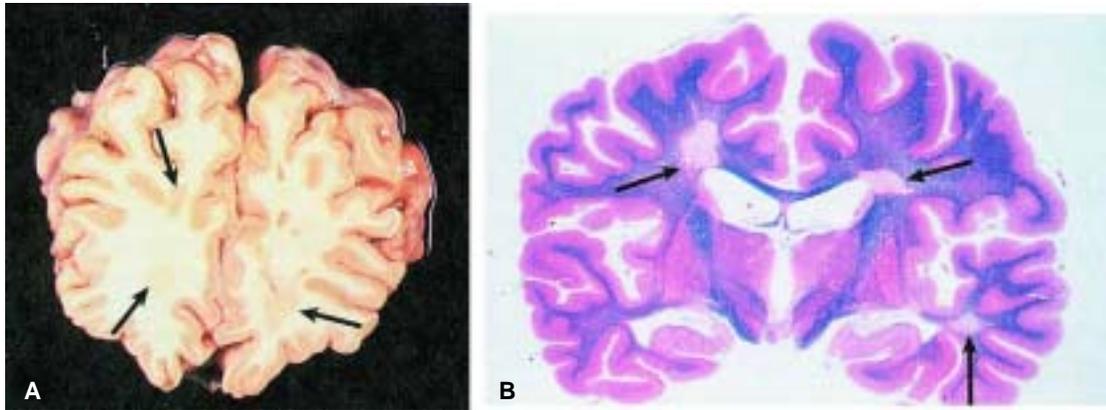
■ **FIGURE 38-16** ■ Multiple sclerosis. (**A**) In this unfixed brain, the plaques of multiple sclerosis in the white matter (*arrows*) assume the darker color of the cerebral cortex. (**B**) A coronal section of the brain from a patient with long-standing multiple sclerosis, which has been stained for myelin, shows discrete areas of demyelination (*arrows*) with characteristic involvement of the superior angles of the lateral ventricles. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1497]. Philadelphia: Lippincott Williams & Wilkins)

Paresthesias are evidenced as numbness, tingling, a burning sensation, or pressure on the face or involved extremities; symptoms can range from annoying to severe. Pain from spasticity also may be a factor that can be aided by appropriate stretching exercises. Other common symptoms are abnormal gait, bladder and sexual dysfunction, vertigo, nystagmus, fatigue, and speech disturbance. These symptoms usually last for several days to weeks, and then completely or partially resolve. After a period of normal or relatively normal function, new symptoms appear. Psychological manifestations, such as mood swings, may represent an emotional reaction to the nature of the disease or, more likely, involvement of the white matter of the cerebral cortex. Depression, euphoria, inattentiveness, apathy, forgetfulness, and loss of memory may occur. Fatigue is one of the most common problems for persons with MS. It often is described as a generalized low-energy feeling not related to depression and different from weakness.

The course of the disease may fall into one of four categories: relapsing-remitting, secondary progressive, primary progressive, or progressive relapsing.[31,32] The *relapsing-remitting* form of the disease is characterized by episodes of acute worsening with recovery and a stable course between relapses. *Secondary progressive disease* involves a gradual neurologic deterioration with or without superimposed acute relapses in a person with previous relapsing-remitting disease. *Primary progressive disease* is characterized by nearly continuous neurologic deterioration from onset of symptoms. The *progressive relapsing category* of disease involves gradual neurologic deterioration from the onset of symptoms but with subsequent superimposed relapses.

Diagnosis

The diagnosis of MS is based on established clinical, MRI, and laboratory findings in cerebrospinal fluid analysis. Examination of the cerebrospinal fluid is used for detecting signs of inflammation and immune responses. A large percentage of patients with MS have elevated immunoglobulin G (IgG) levels, and some have oligoclonal patterns (*i.e.*, discrete electrophoretic bands) even with normal IgG levels. Total protein or lymphocyte levels may be mildly elevated in the cerebrospinal fluid. These test results can be altered in a variety of inflammatory neurologic disorders and are not specific for MS. Advances in MRI have greatly simplified the diagnosis and evaluation of MS. MRI studies can detect the multiplicity of lesions even when CT scans appear normal. A computer-assisted method of MRI can measure lesion size. Many new areas of myelin abnormality are asymptomatic. Serial MRI studies can be done to detect asymptomatic lesions, monitor the progress of existing lesions, and evaluate the effectiveness of treatment. Electrophysiologic evaluations (*e.g.*, evoked potential studies) and CT scans may assist in the identification and documentation of lesions.

Treatment

Most treatment measures for MS are directed at modifying the course and managing the primary symptoms of the disease. The variety of symptoms, unpredictable course, and lack of specific diagnostic methods have made the evaluation and treatment of MS difficult. Persons who are minimally affected by the disorder require no specific treatment. The person should be encouraged to maintain as healthy a lifestyle as possible, including good nutrition and adequate rest and relaxation. Physical therapy may help maintain muscle tone. Every effort should be made to avoid excessive fatigue, physical deterioration, emotional stress, viral infections, and extremes of environmental temperature, which may precipitate an exacerbation of the disease.

The pharmacologic agents used in the treatment of MS fall into four categories: (1) those used to treat acute symptoms of the disease, (2) those used to modify the course of the disease, (3) those used to interrupt progressive disease, and (4) those used to treat the symptoms of the disorder.[31] Corticosteroids are the mainstay of treatment for acute relapses of MS. These agents are thought to reduce the inflammation, improve nerve conduction, and have important immunologic effects. However, long-term administration does not appear to alter the course of the disease and can have harmful side effects. Adrenocorticotropic hormone (ACTH)

also may be used in treatment of MS. Plasmapheresis has proved beneficial in some cases.

The agents used to modify the course of the disease include interferon beta and glatiramer acetate.[31] Both agents have shown some benefit in reducing exacerbations in persons with relapsing-remitting MS. Interferon beta is a cytokine that acts as an immune enhancer. Glatiramer acetate is a synthetic polypeptide that simulates parts of the myelin basic protein. Although the exact mechanism of action is unknown, the drug seems to block myelin-damaging T cells by acting as a myelin decoy.

Progressive MS may be treated with immunosuppressive drugs such as methotrexate, cyclophosphamide, mitoxantrone, and cyclosporine. The drugs used to treat symptoms of the disease include muscle relaxants (*e.g.*, dantrolene, baclofen, diazepam), which are used to relieve spasticity; cholinergic drugs, which are used to treat bladder problems; and antidepressant drugs, which are used for depression.

In summary, UMNs and LMNs innervate the skeletal muscles and are essential for motor function. Amyotrophic lateral sclerosis is a mixed UMN and LMN disorder. Degeneration and loss of neurons in the UMNs in the primary motor cortex leads to loss of fibers within the corticospinal tract and lateral and anterior columns of the spinal cord. Disease of the LMNs leads to weakness, fasciculations, and atrophy of the affected muscle. A remarkable feature of the disease is that the entire sensory system and the intellect remain intact. The neurons for eye movement and the parasympathetic neurons in the sacral spinal cord also are spared. In the more advanced stages, muscles of the palate, pharynx, tongue, neck, and shoulders become involved, causing impairment of chewing, swallowing, and speech. Death usually results from involvement of cranial nerves and respiratory musculature.

MS is an example of a demyelinating disease of the CNS in which there is a slowly progressive breakdown of myelin and formation of plaques but sparing of the axis cylinder of the neuron. Interruption of neural conduction in MS is manifested by a variety of disabling signs and symptoms that depend on the neurons that are affected. The most common symptoms are paresthesias, optic neuritis, and motor weakness. The disease usually is characterized by exacerbations and remissions. Initially, near-normal function returns between exacerbations. The variety of symptoms, course of the disease, and lack of specific diagnostic tests make diagnosis and treatment of the disease difficult.

SPINAL CORD INJURY

Spinal cord injury (SCI) represents damage to the neural elements of the spinal cord. SCI is a disorder primarily of young adults, the most common cause being motor vehicle accidents, followed by falls, violence, sports injuries, and other types of injuries, including attempted suicide and occupational injuries. Of sports-related injuries, 66% are from diving.[33]

Most spinal cord injuries involve damage to the vertebral column and or supporting ligaments as well as the spinal cord. Because of extensive tract systems that connect sensory afferent neurons and LMNs with high brain centers, spinal cord injuries commonly involve both sensory and motor function.

Injury to the Vertebral Column

Injuries to the vertebral column include fractures, dislocations, and subluxations. A fracture can occur at any part of the bony vertebrae, causing fragmentation of the bone. It most often involves the pedicle, lamina, or processes (*e.g.*, facets). Dislocation or subluxation (partial dislocation) injury causes the vertebral bodies to become displaced, with one overriding another and preventing correct alignment of the vertebral column. Damage to the ligaments or bony vertebrae may make the spine unstable. In an unstable spine, further unguarded movement of the spinal column can impinge on the spinal canal, causing compression or overstretching of neural tissue.

Most injuries result from some combination of compressive force or bending movement. Flexion injuries occur when forward bending of the spinal column exceeds the limits of normal movement. A typical flexion injury results when the head is struck from behind, such as in a fall with the back of the head as the point of impact. Extension injuries occur with excessive forced bending (*i.e.*, hyperextension) of the spine backward. A typical extension injury involves a fall in which the chin or face is the point of impact, causing hyperextension of the neck. Injuries of flexion and extension occur more commonly in the cervical spine (C4 to C6) than in any other area. Limitations imposed by the ribs, spinous processes, and joint capsules in the thoracic and lumbar spine make this area less flexible and less susceptible to flexion and extension injuries than the cervical spine.

A compression injury, causing the vertebral bones to shatter, squash, or even burst, occurs when there is spinal loading from a high-velocity blow to the top of the head or when landing forcefully on the feet (38-17A). This typically occurs at the cervical level (*e.g.*, diving injuries) or in the thoracolumbar area (*e.g.*, falling from a distance and landing on the feet). Compression injuries may occur when the vertebrae are weakened by conditions such as osteoporosis and cancer with bone metastasis. Axial rotation injuries can produce highly unstable injuries. Maximal axial rotation occurs in the cervical region, especially between C1 and C2 and at the lumbosacral joint (Fig. 38-17B). Coupling of vertebral motions is common in injury when two or more individual motions occur (*e.g.*, lateral bending and axial rotation).

Types and Classification of Spinal Cord Injury

Spinal cord injury involves damage to the neural elements of the spinal cord. The damage may result from direct trauma to the cord from penetrating wounds or indirect injury resulting from vertebral fractures, fracture-dislocations, or subluxations of the spine. The spinal cord may be contused, not only at the site of injury, but also above and below the trauma site (Fig. 38-18). Traumatic injury may be complicated by blood flow to the cord, with resulting infarction.

Primary and Secondary Injuries
The pathophysiology of SCI can be divided into two types: primary and secondary.[5,34] The *primary neurologic injury* occurs at the time of mechanical injury and is irreversible. It is charac-
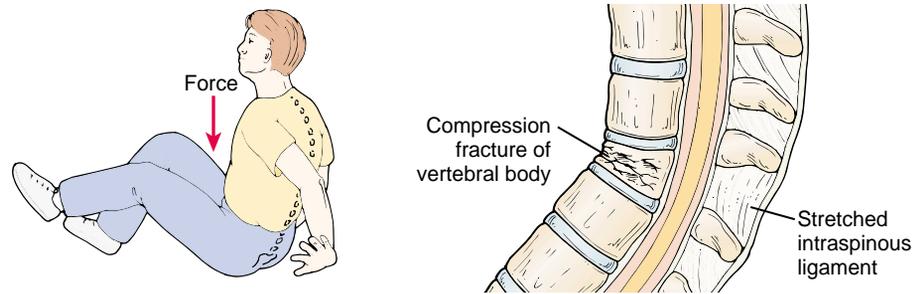
■ **FIGURE 38-17** ■ (**A**) Compression vertebral fracture secondary to axial loading as occurs when a person falls from a height and lands on the buttocks. (**B**) Rotational injury, in which there is concurrent fracture and tearing of the posterior ligamentous complex, is caused by extreme lateral flexion or twisting of the head or neck.
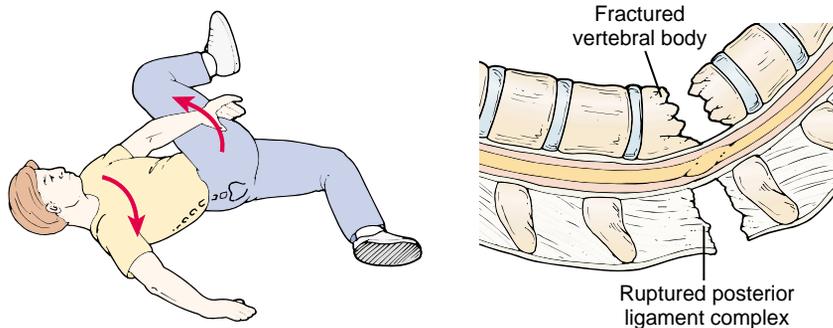
■ **FIGURE 38-18** ■ Cervical contusion. Hyperflexion injury caused forward angulation of the cervical cord, with fracture of the anterior lip of the underlying vertebral body. The cord is angulated over the superior-posterior ridge of the fixed underlying cervical body. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1465]. Philadelphia: Lippincott Williams & Wilkins)

terized by small hemorrhages in the gray matter of the cord, followed by edematous changes in the white matter that lead to necrosis of neural tissue. This type of pathology results from the forces of compression, stretch, and shear associated with fracture or compression of the spinal vertebrae, dislocation of vertebrae (*e.g.*, flexion, extension, subluxation), and contusions caused by jarring of the cord in the spinal canal. Penetrating injuries produce lacerations and direct trauma to the cord and may occur with or without spinal column damage. Lacerations occur when there is cutting or tearing of the spinal cord, which injures nerve tissue and causes bleeding and edema.

Secondary injuries follow the primary injury and promote the spread of injury. Although there is considerable debate about the pathogenesis of secondary injuries, the tissue destruction that occurs ends in progressive neurologic damage. After SCI, several pathologic mechanisms come into play, including vascular damage, neuronal injury that leads to loss of reflexes below the level of injury, and release of vasoactive agents and cellular enzymes. Vascular pathology (*i.e.*, vessel trauma and hemorrhage) can lead to ischemia, increased vascular permeability, and edema. Blood flow to the spinal cord may be further compromised by spinal shock that results from a loss of vasomotor tone and neural reflexes below the level of injury. The release of vasoactive substances (*i.e.*, norepinephrine, serotonin, dopamine, and histamine) from the wound tissue causes vasospasm and impedes blood flow in the microcirculation, producing further necrosis of blood vessels and neurons. The release of proteolytic and lipolytic enzymes from injured cells causes delayed swelling, demyelination, and necrosis in the neural tissue in the spinal cord.

Classification

Alterations in body function that result from SCI depend on the level of injury and the amount of cord involvement. *Tetraplegia*, sometimes referred to as quadriplegia, is the impairment or loss of motor or sensory function (or both) after damage to neural structures in the cervical segments of the spinal cord.[35] It results in impairment of function in the arms, trunk, legs, and pelvic organs (see Fig. 38-7). *Paraplegia* refers to impairment or loss of motor or sensory function (or both) in the thoracic, lumbar, or sacral segments of the spinal cord from damage of neural elements in the spinal canal. With paraplegia, arm functioning is spared, but depending on the level of injury, functioning of the trunk, legs, and pelvic organs may be involved. Paraplegia includes conus medullaris and cauda equina injuries (to be discussed).

Further definitions of SCI describe the extent of neurologic damage as *complete* or *incomplete*. The prognosis for return of function is better in an incomplete injury because of preservation of axonal function.

Incomplete Spinal Cord Injuries. Incomplete SCI implies there is some residual motor or sensory function below the level of injury.[36] Incomplete injuries may manifest in a variety of patterns but can be organized into certain patterns or "syndromes" that occur more frequently and reflect the predominant area of the cord that is involved. Types of incomplete lesions include the central cord syndrome, anterior cord syndrome, Brown-Séquard syndrome, and the conus medullaris syndrome.

A condition called *central cord syndrome* occurs when injury is predominantly in the central gray or white matter of the cord[5] (Fig. 38-19). Because the corticospinal tract fibers are or-ganized with those controlling the arms located more centrally and those controlling the legs located more laterally, some external axonal transmission may remain intact. Motor function of the upper extremities is affected, but the lower extremities may not be affected or may be affected to a lesser degree, with some sparing of sacral sensation. Bowel, bladder, and sexual functions usually are affected to various degrees and may parallel the degree of lower extremity involvement. This syndrome occurs almost exclusively in the cervical cord, rendering the lesion a UMN lesion with spastic paralysis. Central cord damage is more common in elderly persons with narrowing or stenotic changes in the spinal canal that are related to arthritis. Damage also may occur in persons with congenital stenosis.

Anterior artery or *anterior cord syndrome* usually is caused by damage from infarction of the anterior spinal artery, resulting in damage to the anterior two thirds of the cord[5] (Fig. 38-20). The deficits result in loss of motor function provided by the corticospinal tracts and loss of pain and temperature sensation from damage to the lateral spinothalamic tracts. The posterior one third of the cord is relatively unaffected, preserving the dorsal column axons that convey position, vibration, and touch sensation.

A condition called *Brown-Séquard syndrome* results from damage to a hemisection of the anterior and posterior cord[5] (Fig. 38-21). The effect is a loss of voluntary motor function from the corticospinal tract, proprioception loss from the ipsilateral side of the body, and contralateral loss of pain and temperature sensation from the lateral spinothalamic tracts for all levels below the lesion.

Conus medullaris syndrome involves damage to the conus medullaris or the sacral cord (*i.e.*, conus) and lumbar nerve
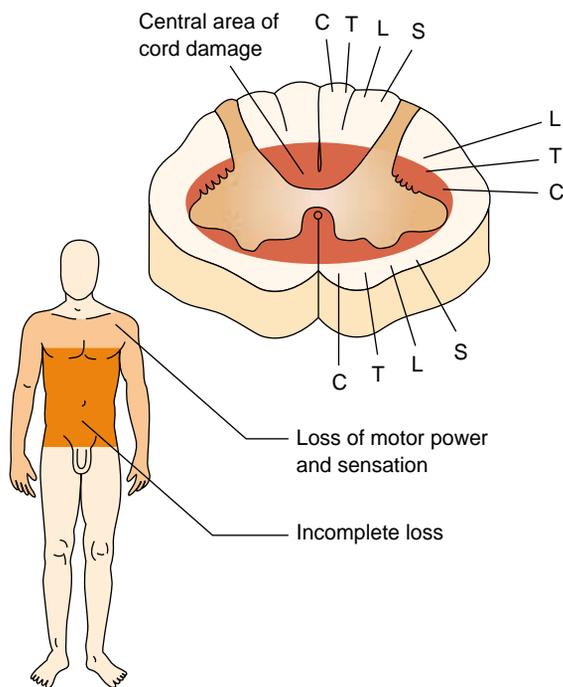
■ FIGURE 38-19 ■ Central cord syndrome. A cross-section of the cord shows central damage and the associated motor and sensory loss. (C, cervical; T, thoracic; L, lumbar; S, sacral). (Hickey J.V. [2003]. *The clinical practice of neurological and neurosurgical nursing* [5th ed., p. 420]. Philadelphia: Lippincott Williams & Wilkins)
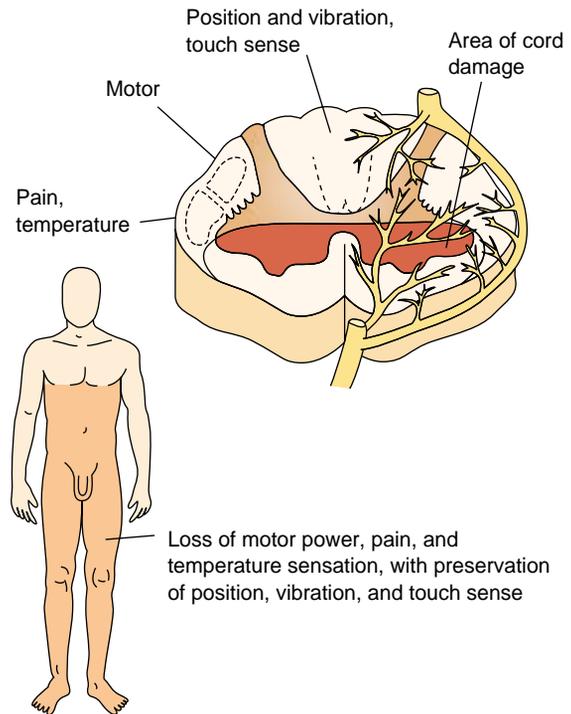
■ FIGURE 38-20 ■ Anterior cord syndrome. Cord damage and associated motor and sensory loss are illustrated. (Hickey J.V. [2003]. *The clinical practice of neurological and neurosurgical nursing* [5th ed., p. 420]. Philadelphia: Lippincott Williams & Wilkins)

Right   Left

Area of cord damage

Loss of pain and
temperature sensation
on opposite side

Loss of voluntary motor
control on the same side
as the cord damage
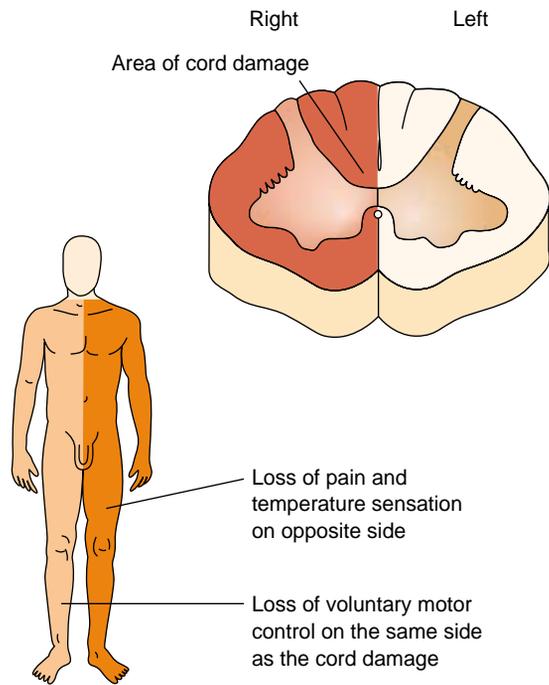
■ **FIGURE 38-21** ■ Brown-Séquard syndrome. Cord damage and associated motor and sensory loss are illustrated. (Hickey J.V. [2003]. *The clinical practice of neurological and neurosurgical nursing* [5th ed., p. 421]. Philadelphia: Lippincott Williams & Wilkins)

roots in the neural canal. Functional deficits resulting from this type of injury usually result in flaccid bowel, bladder, and sexual function. Sacral segments occasionally show preserved reflexes if only the conus is affected. Motor function in the legs and feet may be impaired without significant sensory impairment. Damage to the lumbosacral nerve roots in the spinal canal usually results in LMN and sensory neuron damage known as *cauda equina syndrome*. Functional deficits present as various patterns of asymmetric flaccid paralysis, sensory impairment, and pain.

Complete Spinal Cord Injuries. Complete SCI implies there is an absence of motor and sensory function below the level of injury. Complete cord injuries can result from severance of the cord, disruption of nerve fibers although they remain intact, or interruption of blood supply to that segment, resulting in complete destruction of neural tissue and UMN or LMN paralysis. Approximately 3% of persons with signs of complete injuries on initial examination experience some recovery within 24 hours.[36]

Acute Spinal Cord Injury

Sudden complete transection of the spinal cord results in complete loss of motor, sensory, reflex, and autonomic function below the level of injury. This immediate response to spinal cord injury is often referred to as *spinal cord shock*. It is characterized by flaccid paralysis with loss of tendon reflexes below the level of injury, absence of somatic and visceral sensations below the level of injury, and loss of bowel and bladder function. Loss of systemic sympathetic vasomotor tone may result in vasodilation, increased venous capacity, and hypotension. These manifestations occur regardless of whether the level of

the lesion eventually will produce spastic (UMN) or flaccid (LMN) paralysis. The basic mechanisms accounting for transient spinal shock are unknown. Spinal shock may last for hours, days, or weeks. Usually, if reflex function returns by the time the person reaches the hospital, the neuromuscular changes are reversible. This type of reversible spinal shock may occur in football-type injuries, in which jarring of the spinal cord produces a concussion-like syndrome with loss of movement and reflexes, followed by full recovery within days. In persons in whom the loss of reflexes persists, hypotension and bradycardia may become critical but manageable problems. In general, the higher the level of injury, the greater is the effect.

Management. The goal of management of acute SCI is to reduce the neurologic deficit and prevent any additional loss of neurologic function. The specific steps in resuscitation and initial evaluation can be carried out at the trauma site or in the emergency room, depending on the urgency of the situation.[34,37] Most traumatic injuries to the spinal column render it unstable, mandating measures such as immobilization with collars and backboards and limiting the movement of persons at risk for or with known SCI. Every person with multiple trauma or head injury, including victims of traffic and sporting accidents, should be suspected of having sustained an acute SCI.[34,37]

The nature of the injury determines further methods of stabilization and treatment. In unstable injuries of the cervical spine, cervical traction improves or restores spinal alignment, decompresses neural structures, and facilitates recovery. Fractures and dislocations of the thoracic and lumbar vertebrae may be initially stabilized by restricting the person to bed rest and turning him or her in a log-rolling manner to keep the spine rigid. Gunshot or stab wounds of the spinal column may not produce structural instability and require immobilization. The goal of early surgical intervention for an unstable spine is to provide internal skeletal stabilization so that early mobilization and rehabilitation can occur.

One of the more important aspects of early SCI care is the prevention and treatment of spinal or systemic shock and the hypoxia associated with compromised respiration. Correcting hypotension or hypoxia is essential to maintaining circulation to the injured cord.[38] The use of high-dose methylprednisolone has been shown to improve the outcome from SCI when given shortly after injury. Methylprednisolone is a short-acting corticosteroid that has been used extensively in the treatment of inflammatory and allergic disorders. In acute SCI, it is thought to stabilize cell membranes, enhance impulse generation, improve blood flow, and inhibit free radical formation.

Disruption of Functional Abilities

Functional abilities after SCI are subject to various degrees of somatosensory and skeletal muscle function loss and altered reflex activity based on the level of cord injury and extent of cord damage (Table 38-2).

Somatosensory and Skeletal Muscle Function

Motor function in cervical injuries ranges from complete dependence to independence with or without assistive devices in activities of mobility and self-care. The functional levels of cervical injury are related to C5, C6, C7, or C8 innervation. At the

TABLE 38-2	Functional Abilities by Level of Cord Injury			
Injury Level	Segmental Sensorimotor Function	Dressing, Eating	Elimination	Mobility*
C1	Little or no sensation or control of head and neck; no diaphragm control; requires continuous ventilation	Dependent	Dependent	Limited. Voice or sip-n-puff controlled electric wheelchair
C2 to C3	Head and neck sensation; some neck control. Independent of mechanical ventilation for short periods	Dependent	Dependent	Same as for C1
C4	Good head and neck sensation and motor control; some shoulder elevation; diaphragm movement	Dependent; may be able to eat with adaptive sling	Dependent	Limited to voice, mouth, head, chin, or shoulder-controlled electric wheelchair
C5	Full head and neck control; shoulder strength; elbow flexion	Independent with assistance	Maximal assistance	Electric or modified manual wheelchair, needs transfer assistance
C6	Fully innervated shoulder; wrist extension or dorsiflexion	Independent or with minimal assistance	Independent or with minimal assistance	Independent in transfers and wheelchair
C7 to C8	Full elbow extension; wrist plantar flexion; some finger control	Independent	Independent	Independent; manual wheelchair
T1 to T5	Full hand and finger control; use of intercostal and thoracic muscles	Independent	Independent	Independent; manual wheelchair
T6 to T10	Abdominal muscle control, partial to good balance with trunk muscles	Independent	Independent	Independent; manual wheelchair
T11 to L5	Hip flexors, hip abductors (L1–3); knee extension (L2–4); knee flexion and ankle dorsiflexion (L4–5)	Independent	Independent	Short distance to full ambulation with assistance
S1 to S5	Full leg, foot, and ankle control; innervation of perineal muscles for bowel, bladder, and sexual function (S2–4)	Independent	Normal to impaired bowel and bladder function	Ambulate independently with or without assistance

*Assistance refers to adaptive equipment, setup, or physical assistance.

C5 level, deltoid and biceps function is spared, allowing full head, neck, and diaphragm control with good shoulder strength and full elbow flexion. At the C6 level, wrist dorsiflexion by the way of wrist extensors is functional, allowing tenodesis, which is the natural bending inward and flexion of the fingers when the wrist is extended and bent backward. Tenodesis is a key movement because it can be used to pick up objects when finger movement is absent. A functional C7 injury allows full elbow flexion and extension, wrist plantar flexion, and some finger control. At the C8 level, finger flexion is added.

Thoracic cord injuries (T1 to T12) allow full upper extremity control with limited to full control of intercostal and trunk muscles and balance. Injury at the T1 level allows full fine motor control of the fingers. Because of the lack of specific functional indicators at the thoracic levels, the level of injury usually is determined by sensory level testing.

Functional capacity in the L1 through L5 nerve innervations allows hip flexors, hip abductors (L1 to L3), movement of the knees (L2 to L5), and ankle dorsiflexion (L4 to L5). Sacral (S1 to S5) innervation allows for full leg, foot, and ankle control and innervation of perineal musculature for bowel, bladder, and sexual function.

Altered Reflex Activity. Spinal cord reflexes are fully integrated within the spinal cord and can function independent of input from higher centers. Altered spinal reflex activity after SCI is essentially determined by the level of injury and whether UMNs or LMNs are affected. With UMN injuries at T12 and above, the cord reflexes remain intact, while communication

pathways with higher centers have been interrupted. This results in spasticity of involved skeletal muscle groups and of smooth and skeletal muscles that control bowel, bladder, and sexual function. In LMN injuries at T12 or below, the reflex circuitry itself has been damaged at the level of the spinal cord or spinal nerve, resulting in a decrease or absence of reflex function. The LMN injuries cause flaccid paralysis of involved skeletal muscle groups and the smooth and skeletal muscles that control bowel, bladder, and sexual function. However, injuries near the T12 level may result in mixed UMN and LMN deficits (*e.g.*, spastic paralysis of the bowel and bladder with flaccid muscle tone).

After the period of spinal shock in a UMN injury, isolated spinal reflex activity and muscle tone that is not under the control of higher centers returns. This may result in hypertonia and spasticity of skeletal muscles below the level of injury. These spastic movements are involuntary, instead of voluntary, a distinction that needs to be explained to persons with SCI and their families. The antigravity muscles, the flexors of the arms and extensors of the legs, are predominantly affected. Spastic movements usually are heightened initially after injury, reaching a peak and then becoming stable in approximately 2 years.

The stimuli for reflex muscle spasm arise from somatic and visceral afferent pathways that enter the cord below the level of injury. The most common of these stimuli are muscle stretching, bladder infections or stones, fistulas, bowel distention or impaction, pressure areas or irritation of the skin, and infections. Because the stimuli that precipitate spasms vary from person to person, careful assessment needs to be done to iden-

tify the factors that precipitate spasm in each person. Passive range-of-motion exercises to stretch the spastic muscles help to prevent spasm induced by muscle stretching such as occurs with change in body position.

Spasticity in and of itself is not detrimental and may even facilitate maintenance of muscle tone to prevent muscle wasting, improve venous return, and aid in mobility. Spasms become detrimental when they impair safety or reduce the ability to make functional gains in mobility and activities of daily living. Spasms also may cause trauma to bones and tissues, leading to joint contractures and skin breakdown.

Respiratory Muscle Function. Ventilation requires movement of the expiratory and inspiratory muscles, all of which receive innervation from the spinal cord. The main muscle of ventilation, the diaphragm, is innervated by segments C3 to C5 through the phrenic nerves. The intercostal muscles, which function in elevating the rib cage and are needed for coughing and deep breathing, are innervated by spinal segments T1 through T7. The major muscles of expiration are the abdominal muscles, which receive their innervation from levels T6 to T12.

Although the ability to inhale and exhale may be preserved at various levels of SCI, functional deficits in ventilation are most apparent in the quality of the breathing cycle and the ability to oxygenate tissues, eliminate carbon dioxide, and mobilize secretions. Cord injuries involving C1 to C3 result in a lack of respiratory effort, and affected patients require assisted ventilation. Although a C3 to C5 injury allows partial or full diaphragmatic function, ventilation is diminished because of the loss of intercostal muscle function, resulting in shallow breaths and a weak cough. Below the C5 level, as less intercostal and abdominal musculature is affected, the ability to take a deep breath and cough is less impaired. Maintenance therapy consists of muscle training to strengthen existing muscles for endurance and mobilization of secretions. The ability to speak is compromised with assisted ventilation, whether continuous or intermittent. Thus, ensuring adequate communication of needs is also essential.

Autonomic Nervous System Function

In addition to its effects on skeletal muscle function, SCI interrupts ANS function below the site of injury. This includes sympathetic outflow from the thoracic and lumbar cord and parasympathetic outflow from the sacral cord. Because of their site of exit from the CNS, the cranial nerves, such as the vagus, are unaffected. Dependent upon the level of injury, the spinal reflexes that control ANS function are largely isolated from the rest of the CNS. Afferent sensory input that enters the spinal cord is unaffected, as is the efferent motor output from the cord. Lacking is the regulation and integration of reflex function by centers in the brain and brain stem. This results in a situation in which the autonomic reflexes below the level of injury are uncontrolled, while those above the level of injury function in a relatively controlled manner.

The sympathetic nervous system regulation of circulatory function and thermoregulation present some of the most severe problems in SCI. The higher the level of injury and the greater the surface area affected, the more profound are the effects on circulation and thermoregulation. Persons with injury at the T6 level or above experience problems in regulating vasomotor tone; those with injuries below the T6 level usually have sufficient sympathetic function to maintain adequate vasomotor function. The level of injury and its corresponding problems may vary among persons, and some dysfunctional effects may be seen at levels below T6. With lower lumbar and sacral injuries, sympathetic function remains essentially unaltered.

The Vasovagal Response. The vagus nerve (cranial nerve X) normally exerts a continuous inhibitory effect on heart rate. Vagal stimulation that causes a marked bradycardia by way of the vagus nerve is called the *vasovagal response*. Visceral afferent input to the vagal centers in the brain stem of persons with tetraplegia or high-level paraplegia can produce marked bradycardia when unchecked by a dysfunctional sympathetic nervous system. Severe bradycardia and even asystole can result when the vasovagal response is elicited by deep endotracheal suctioning or rapid position change. Preventive measures, such as hyperoxygenation before, during, and after suctioning, are advised. Rapid position changes should be avoided or anticipated, and anticholinergic drugs should be immediately available to counteract severe episodes of bradycardia.

Autonomic Dysreflexia. Autonomic dysreflexia, also known as *autonomic hyperreflexia*, represents an acute episode of exaggerated sympathetic reflex responses that occur in persons with injuries at T6 and above, in which CNS control of sympathetic responses is lost (see Fig. 38-22). It does not occur until spinal shock has resolved and autonomic reflexes return, most often within the first 6 months after injury. It is most unpredictable during the first year after injury but can occur throughout the person's lifetime.

Autonomic dysreflexia, is characterized by vasospasm, hypertension ranging from mild (20 mm Hg above baseline) to severe (as high as 240/120 mm Hg or higher), skin pallor, and goose flesh associated with the piloerector response. Because baroreceptor function and parasympathetic control of heart rate travels by way of the cranial nerves, these responses remain intact. Continued hypertension produces a baroreflex-mediated vagal slowing of the heart rate to bradycardic levels. There is an accompanying baroreflex-mediated vasodilatation with flushed skin and profuse sweating above the level of injury, headache ranging from dull to severe and pounding, nasal stuffiness, and feelings of anxiety. A person may experience one, several, or all of the symptoms with each episode.

The stimuli initiating the dysreflexic response include visceral distention, such as a full bladder or rectum; stimulation of pain receptors, such as occurs with pressure ulcers, ingrown toenails, dressing changes, and diagnostic or operative procedures; and visceral contractions, such as ejaculation, bladder spasms, or uterine contractions. In many cases, the dysreflexic response results from a full bladder.

Autonomic dysreflexia is a clinical emergency, and without prompt and adequate treatment, convulsions, loss of consciousness, and even death can occur. The major components of treatment include monitoring blood pressure while removing or correcting the initiating cause or stimulus. The person should be placed in an upright position, and all support hose or binders should be removed to promote venous pooling of blood and reduce venous return, thereby decreasing blood pressure. If the stimuli have been removed or the stimuli cannot
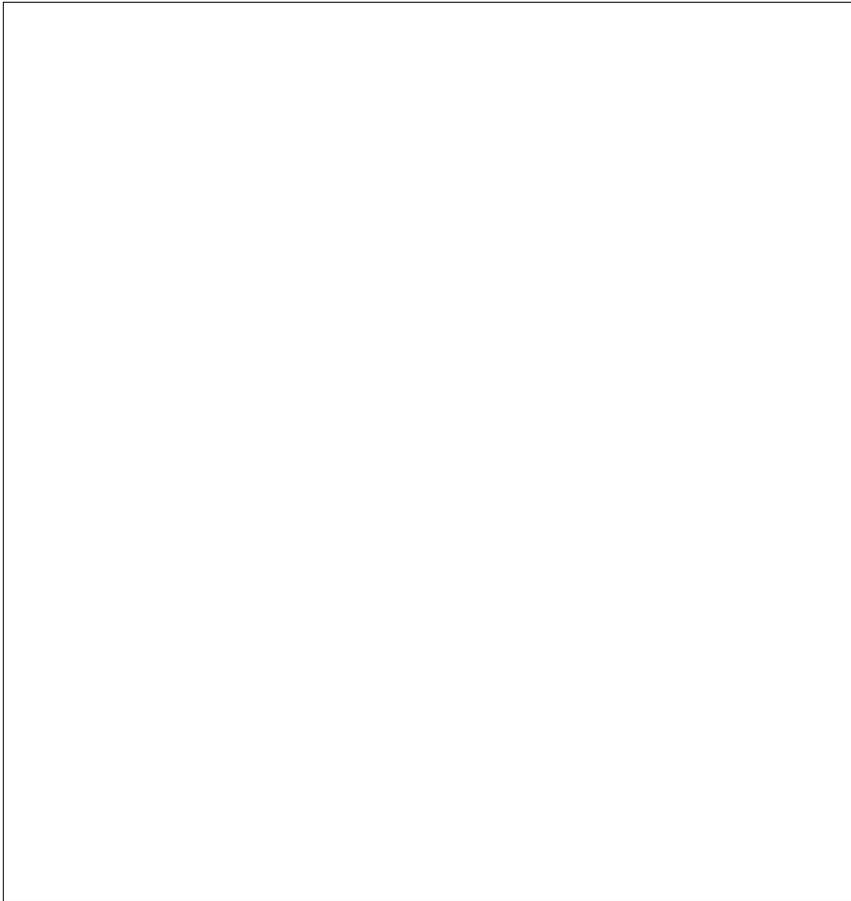
■ **FIGURE 38-22** ■ Mechanisms of autonomic hyperreflexia.

be identified and the upright position is established but the blood pressure remains elevated, drugs that block autonomic function are administered. Prevention of the type of stimuli that trigger the dysreflexic event is advocated.

Postural Hypotension. Postural, or orthostatic, hypotension usually occurs in persons with injuries at T4 to T6 and above and is related to the interruption of descending control of sympathetic outflow to blood vessels in the extremities and abdomen. Pooling of blood, along with gravitational forces, impairs venous return to the heart, and there is a subsequent decrease in cardiac output when the person is placed in an upright position. The signs of orthostatic hypotension include dizziness, pallor, excessive sweating above the level of the lesion, complaints of blurred vision, and possibly fainting. Postural hypotension usually is prevented by slow changes in position and measures to promote venous return.

Other Functions

Edema and Deep Vein Thrombosis. Edema and deep vein thrombosis are common problems in persons with SCI. The development of edema is related to decreased peripheral vascular resistance, areflexia or decreased tone in the paralyzed limbs, and immobility that causes increased venous pressure and abnormal pooling of blood in the abdomen, lower limbs, and upper extremities. Edema in the dependent body parts usually is relieved by positioning to minimize gravitational forces or by using compression devices (*e.g.*, support stockings, binders) that encourage venous return.

Deep vein thrombosis also is of concern because of the venous pooling and loss of skeletal muscle movement below the level of injury. Although it is seen more frequently in the postacute phase of SCI, it often has its origin during the events surrounding the initial injury. Prevention includes assessment of risk and measures to prevent venous pooling of blood, especially in the paralyzed limbs (*e.g.*, range-of-motion exercises and vascular compression devices).

Bladder, Bowel, and Sexual Function. Among the most devastating consequences of SCI is the loss of bowel and bladder function. Loss of bladder function results from disruption of neural pathways between the bladder and the reflex voiding center at the S2 to S4 level (*i.e.*, an LMN lesion) or between the reflex voiding center and higher brain centers for communication and coordinated sphincter control (*i.e.*, a UMN lesion). Persons with UMN lesions or spastic bladders lack awareness of bladder filling (*i.e.*, storage) and voluntary control of voiding (*i.e.*, evacuation). In LMN lesions or flaccid bladder dysfunction, lack of awareness of bladder filling and lack of bladder tone render the person unable to void voluntarily or involuntarily.

Bowel elimination is a coordinated function involving the enteric nervous system, the ANS, and the CNS. Persons with SCI above S2 to S4 develop spastic functioning of the defecation reflex and loss of voluntary control of the external anal sphincter. Damage to the cord at the S2 to S4 level causes flaccid functioning of the defecation reflex and loss of anal sphincter tone. Even though the enteric nervous system innervation

1 LINE

of the bowel remains intact, without the defecation reflex, peristaltic movements are ineffective in evacuating stool.

Sexual function, as in bladder and bowel control, is mediated by the S2 to S4 segments of the spinal cord. The genital sexual response in SCI, which is manifested by an erection in men and vaginal lubrication in women, may be initiated by mental or touch stimuli, depending on the level of injury. The T11 to L2 cord segments have been identified as the mental-stimuli, or psychogenic, sexual response area, where autonomic nerve pathways in communication with the forebrain leave the cord and innervate the genitalia. The S2 to S4 cord segments have been identified as the sexual-touch reflex center. In T10 or higher injuries (UMN lesion), reflex sexual response to genital touch may occur freely. However, a sexual response to mental stimuli (T11 to L2) does not occur because of the spinal lesion blocking the communication pathway. In an injury at T12 or below (LMN lesion), the sexual reflex center may be damaged, and there may be no response to touch.

In men, the lack of erectile ability or inability to experience penile sensations or orgasm is not a reliable indicator of fertility, which should be evaluated by an expert. In women, fertility is parallel to menses; usually, it is delayed 3 months to 5 months after injury. There are hazards to pregnancy, labor, and birth control devices relative to SCI that require knowledgeable health care providers.

Skin Integrity. The entire surface of the skin is innervated by cranial or spinal nerves organized into dermatomes that show cutaneous distribution. The CNS and ANS also play a vital role in skin function. The sympathetic nervous system, through control of vasomotor and sweat gland activity, influences the health of the skin by providing adequate circulation, excretion of body fluids, and temperature regulation. The lack of sensory warning mechanisms and voluntary motor ability below the level of injury, coupled with circulatory changes, place the person with SCI at major risk for disruption of skin integrity. Significant factors associated with disruption of skin integrity are pressure, shearing forces, and localized trauma and irritation. Relieving pressure, allowing adequate circulation to the skin, and skin inspection are primary ways of maintaining skin integrity. Of all the complications after SCI, skin breakdown is the most preventable.

> **In summary,** spinal cord injury is a disabling neurologic condition most commonly caused by motor vehicle accidents, falls, and sports injuries. Dysfunctions of the nervous system after SCI comprise various degrees of sensorimotor loss and altered reflex activity based on the level of injury and extent of cord damage. Depending on the level of injury, the physical problems of SCI include spinal shock; ventilation and communication problems; ANS dysfunction that predisposes to the vasovagal response, autonomic hyperreflexia, impaired body temperature regulation, and postural hypotension; impaired muscle pump and venous innervation leading to edema of dependent areas of the body and risk of deep vein thrombosis; altered sensorimotor integrity that contributes to uncontrolled muscle spasms, altered pain responses, and threat to skin integrity; alterations in bowel and bladder elimination; and impaired sexual function.

LONG

REVIEW QUESTIONS

■ Define a motor unit and characterize its mechanism of controlling muscle movement.

■ Describe muscle atrophy and differentiate between disuse and degenerative atrophy.

■ Describe the pathology associated with Duchenne muscular dystrophy.

■ Relate the clinical manifestations of myasthenia gravis to its cause.

■ Compare the cause and manifestations of peripheral mononeuropathies with peripheral polyneuropathies.

■ Describe the functional organization of the basal ganglia and communication pathways with the thalamus and cerebral cortex.

■ State the possible mechanisms responsible for the development of Parkinson's disease and characterize the manifestations and treatment of the disorder.

■ Relate the functions of the cerebellum to production of vestibulocerebellar ataxia, decomposition of movement, and cerebellar tremor.

■ Relate the pathologic UMN and LMN changes that occur in amyotrophic lateral sclerosis to the manifestations of the disease.

■ Explain the significance of demyelination and plaque formation in multiple sclerosis.

■ Describe the manifestations of multiple sclerosis.

■ Explain how loss of UMN function contributes to the muscle spasms that occur after recovery from spinal cord injury.

■ State the effects of spinal cord injury on ventilation and communication, the ANS, cardiovascular function, sensorimotor function, and bowel and bladder function.

connection─

Visit the Connection site at **connection.lww.com/go/porth** for links to chapter-related resources on the Internet.

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