is very wide, from motor disturbances to epilepsy, schizophrenia, mood imbalances, cognitive disorders, neurodegeneration, and even aging. The more we learn, the more it becomes apparent that these diseases exert very broad effects that blur the boundaries between their classifications. So-called movement disorders such as Parkinson disease, for example, involve cognitive and affective changes; disorders of cognition such as autism or schizophrenia can have very physical manifestations.

Despite these somewhat fuzzy boundaries, each chapter in this section will examine the principles underlying each major class of disease from the perspective of neuroscience. The emphasis here is on molecular mechanisms, so far as they are currently understood. It is perhaps surprising that so many different disease conditions seem to converge on one physiological point: synaptic function. In autism and several psychiatric disorders, synaptic development goes awry; in epilepsy, abnormal ion channel activity disturbs the balance of synaptic input from excitatory and inhibitory neurons. Aging and neurodegenerative disorders bring about synaptic loss through gradual alterations in protein and RNA homeostasis that tax normal cellular functions.

This observation is offered to help give shape to the material you are about to encounter, but should not be used to oversimplify. Anyone tempted by reductionism would do well to engage with the works of great artists such as Dostoevsky and Van Gogh, who represent the complexities of human experience in all its anguish and glory.

Part Editor: Huda Y. Zoghbi

Part IX

57

Diseases of the Peripheral Nerve and Motor Unit

… to move things is all that mankind can do, for such the sole executant is muscle, whether in whispering a syllable or in felling a forest.

Charles Sherrington, 1924

A major task of the elaborate information processing that takes place in the brain is the contraction of skeletal muscles. The challenge of deciding when and how to move is, to a large degree, the driving force behind the evolution of the nervous system (Chapter 30).

In all but the most primitive animals, movement is generated by specialized muscle cells. There are three general types of muscles: Smooth muscle is used primarily for internal actions such as peristalsis and control of blood flow; cardiac muscle is used exclusively for pumping blood; and skeletal muscle is used primarily for moving bones. In this chapter, we examine a variety of neurological disorders in mammals that affect movement by altering either action potential conduction in a motor nerve, synaptic transmission from nerve to muscle, or muscle contraction itself.

In 1925, Charles Sherrington introduced the term *motor unit* to designate the basic unit of motor function—a motor neuron and the group of muscle fibers it innervates (Chapter 31). The number of muscle fibers innervated by a single motor neuron varies widely throughout the body depending on the dexterity of the movements being controlled and the mass of the body part to be moved. Thus, eye movements are finely controlled by motor units with fewer than 100 muscle

fibers, whereas in the leg, a single motor unit contains up to 1,000 muscle fibers. In each case, all the muscles innervated by a motor unit are of the same type. Moreover, motor units are recruited in a fixed order for both voluntary and reflex movements. The smallest motor units are the first to be recruited, joined later by larger units as muscle force increases.

The motor unit is a common target of disease. The distinguishing features of diseases of the motor unit vary depending on which functional component is primarily affected: (1) the cell body of the motor or sensory neuron, (2) the corresponding axons, (3) the neuromuscular junction (the synapse between the motor axon and muscle), or (4) the muscle fibers innervated by the motor neuron. Accordingly, disorders of the motor unit have traditionally been grouped into motor neuron diseases, peripheral neuropathies, disorders of the neuromuscular junction, and primary muscle diseases (myopathies) (Figure 57–1).

Patients with peripheral neuropathies experience weakness that arises from abnormal function of motor neurons or their axons, although problems with sensation can also occur since most peripheral neuropathies also involve sensory neurons. By contrast, in motor neuron diseases, the motor neurons and motor tracts in the spinal cord degenerate but sensory nerves are spared. In myopathies, weakness is caused by degeneration of the muscles with little or no change in motor neurons. In neuromuscular junction diseases, alterations in the neuromuscular synapse lead to weakness that may be intermittent. Clinical and laboratory studies usually distinguish disorders of peripheral nerves from those of the neuromuscular junction or muscle (Table 57–1).

Disorders of the Peripheral Nerve, Neuromuscular Junction, and Muscle Can Be Distinguished Clinically

When a peripheral nerve is cut, the muscles innervated by that nerve immediately become paralyzed and then waste progressively. Because the nerve carries sensory as well as motor fibers, sensation in the area innervated by the nerve is also lost and tendon reflexes are lost immediately. The term *atrophy* (literally, lack of nourishment) refers to the wasting away of a once-normal muscle; because of historical usage the term appears in the names of several diseases that are now regarded as neurogenic.

The main symptoms of the *myopathies* are due to weakness of skeletal muscle and often include difficulty in walking or lifting. Other less common symptoms include inability of the muscle to relax (myotonia), cramps, pain (myalgia), or the appearance in the urine of the heme-containing protein that gives muscle its red color (myoglobinuria). The *muscular dystrophies* are myopathies with special characteristics: The diseases are inherited, all symptoms are caused by weakness, the weakness becomes progressively more

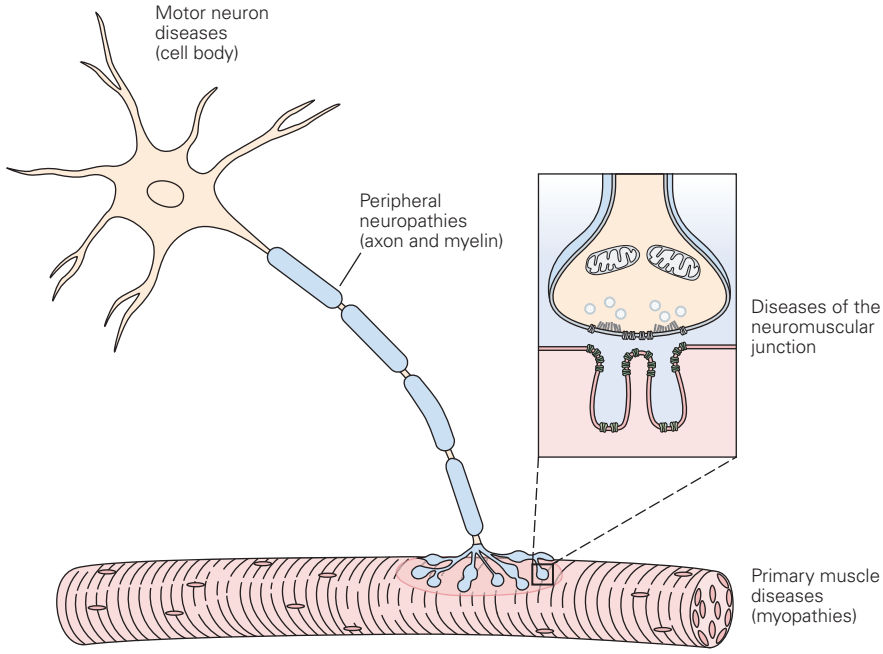

Figure 57–1 The four types of motor unit disorders. Motor unit disorders are categorized according to the part of the motor unit that is affected. Motor neuron diseases affect the cell body of the neuron, while peripheral neuropathies target the axon. Diseases of the neuromuscular junction affect the functioning of the synapse, and myopathies affect muscle fibers.

Table 57–1 Differential Diagnosis of Disorders of the Motor Unit

Finding	Nerve	Neuromuscular junction	Muscle
Clinical			
Weakness	++	+	++
Wasting	++	–	+
Fasciculations	+	–	–
Cramps	+	–	+/–
Sensory loss	+/–	–	–
Hyperreflexia, Babinski	+ (ALS)	–	–
Laboratory			
Elevated serum CPK	–	–	++
Elevated cerebrospinal fluid protein	+/–	–	–
Slowed nerve conduction	+	–	–
Response to repetitive stimulation	Normal	Decremental (MG) Incremental (LEMS)	Normal
Electromyography			
Fibrillation, fasciculation	++	–	+/–
Duration of potentials	Increased	Normal	Decreased
Amplitude of potentials	Increased	Normal	Decreased
Muscle Biopsy			
Isolated fiber atrophy	++	Normal	+/–
Grouped fiber atrophy	++	Normal	Normal
Muscle necrosis	Normal	Normal	++

ALS, amyotrophic lateral sclerosis; CPK, creatine phosphokinase; LEMS, Lambert-Eaton myasthenic syndrome; MG, myasthenia gravis.

severe, and signs of degeneration and regeneration are seen histologically.

Distinguishing neurogenic and myopathic diseases may be difficult because both are characterized by weakness of muscle. As a first approximation, weakness of the distal limbs most often indicates a neurogenic disorder, whereas proximal limb weakness signals a myopathy. The main clinical and laboratory features used for the differential diagnosis of diseases of the motor unit are listed in Table 57–1.

One test that is very helpful is needle electromyography (EMG), a clinical procedure in which a small needle is inserted into a muscle to record extracellularly the electrical activity of several neighboring motor units. Three specific measurements are important: spontaneous activity at rest, the number of motor units under voluntary control, and the duration and amplitude of action potentials in each motor unit. (Normal ranges of values have been established for the amplitude and duration of motor unit potentials; the amplitude is determined by the number of muscle fibers within the motor unit.)

In normal muscle, there is usually no activity outside the end-plate in the muscle at rest. During a weak voluntary contraction, a series of motor unit potentials is recorded as different motor units become recruited. In fully active normal muscles, these abundant potentials overlap in an interference pattern so that it is impossible to identify single potentials (Figure 57–2A).

In neurogenic disease, the partially denervated muscle is spontaneously active even at rest. The muscle may still contract in response to voluntary motor commands, but the number of motor units under voluntary control is smaller than normal because some motor axons have been lost. The loss of motor units is evident in the EMG during a maximal contraction, which shows a pattern of discrete motor unit potentials instead of the profuse interference pattern for normal muscles (Figure 57–2B). In recently denervated muscle, the EMG may also show spontaneous low-amplitude electrical potentials that correspond to the firing of a single muscle fiber, known as fibrillation potentials. As the neurogenic disease progresses, the amplitude and duration of individual motor unit potentials may increase because the remaining axons give off small branches that innervate the muscle fibers denervated

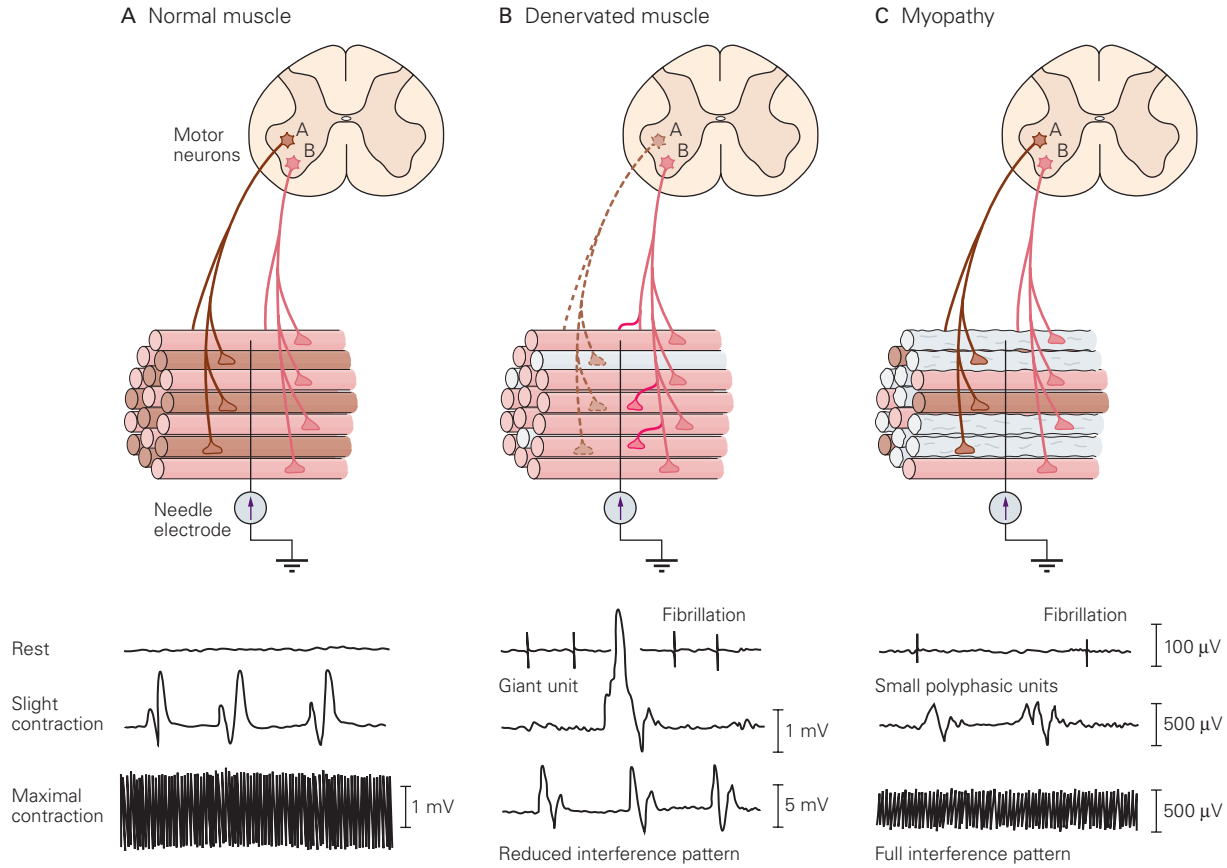

Figure 57–2 Electrical recording from skeletal muscle reveals different profiles in neuropathies and primary muscle diseases.

A. Typical activity in a normal muscle. The muscle fibers innervated by a single motor neuron are usually not adjacent to one another. When a motor unit potential is recorded by a needle electrode inserted into the muscle, the highly effective transmission at the neuromuscular junction ensures that each muscle fiber innervated by the same neuron will generate an action potential and contract in response to an action potential in the motor neuron. In the normal, resting muscle, there is no electrical activity recorded from muscle in the electromyogram (EMG). Slight activation of the muscle by a voluntary movement reveals characteristic extracellular electrical responses in muscle (motor unit potentials (MUPs)). Maximal muscle contraction produces a characteristic complex burst of electrical activity from muscle (the interference pattern).

B. When motor neurons are diseased, the number of motor units under voluntary control is reduced. The muscle fibers supplied by the degenerating motor neuron (cell A) become denervated and atrophic. However, the surviving neuron (cell B) sprouts axonal branches that reinnervate some of the denervated muscle fibers. Axons of the surviving motor neuron fire spontaneously even at rest, giving rise to fasciculations, another characteristic of motor neuron disease. Single denervated fibers also fire spontaneously, producing fibrillations (top trace). With loss of nerve input from motor neuron A and reinnervation of the denervated fibers by motor neuron B, activation of motor neuron B produces an enlarged MUP (giant motor unit). In this setting, there is simplification of the interference pattern.

C. When muscle is diseased (myopathy), the number of muscle fibers in each motor unit is reduced. Some muscle fibers innervated by the two motor neurons shrink and become nonfunctional. In the electromyogram, the motor unit potentials do not decrease in number but are smaller and of longer duration than normal and are polyphasic. Affected single muscle fibers sometimes contract spontaneously, producing fibrillation. When muscle is mildly activated, the MUPs show reduced amplitudes. After maximal muscle contraction, the interference pattern also shows a reduction in amplitude.

by the loss of other axons. Accordingly, surviving motor units contain more than the normal number of muscle fibers.

In myopathic diseases, there is no activity in the muscle at rest and no change in the number of motor units firing during a contraction. But because there are fewer surviving muscle fibers in each motor unit, the motor unit potentials are of longer duration and more complex, with alternating +/− polarity (polyphasic), and are smaller in amplitude (Figure 57–2C).

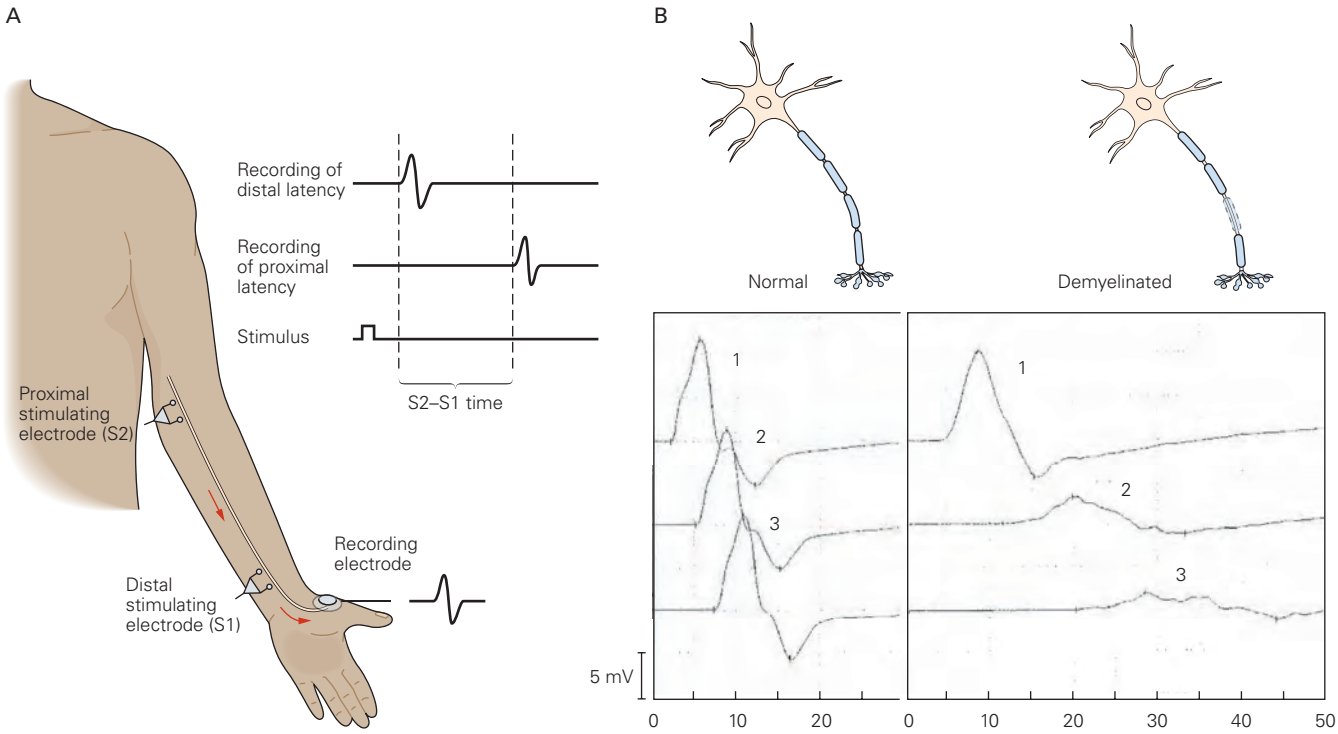

Figure 57–3 Motor nerve conduction velocity can be determined by recording the compound muscle action potential (CMAP) in response to electrical stimulation at different points along the nerve.

A. A shock is applied through a proximal surface stimulating electrode (**S2**) or through a distal stimulating electrode (**S1**), and the extracellular CMAP in the thumb is measured transcutaneously by the recording electrode. The time it takes the action potential to propagate from S2 to the muscle (t_{S2}) is the proximal latency; the time from S1 to the muscle (t_{S1}) is the distal latency. The distance between S1 and S2 divided by ($t_{S2} - t_{S1}$) gives the conduction velocity.

B. The waveforms of the thumb CMAPs elicited by stimulation of the motor nerve at the wrist (**1**), just below the elbow (**2**), and just above the elbow (**3**). In normal subjects (*left*), the waveforms are the same regardless of the site of stimulation. They are distinguished only by the longer time period required for the waveform to develop as the site of the stimulus is moved up the arm (away from the recording site). When the motor nerve is demyelinated between S1 and S2 but above the wrist, the CMAP is normal when stimulation occurs at the wrist (**1**) but delayed and desynchronized when stimulation is proximal to the nerve lesion (**2**, **3**). (Adapted, with permission, from Bromberg 2002.)

The conduction velocities of peripheral motor axons can also be measured through electrical stimulation and recording (see Figure 57–3). The conduction velocity of motor axons is slowed in demyelinating neuropathies but is normal in neuropathies without demyelination (axonal neuropathies).

Another test that helps to distinguish myopathic from neurogenic diseases is the measurement of serum enzyme activities. The sarcoplasm of muscle is rich in soluble enzymes that are normally found in low concentrations in the serum. In many muscle diseases, the concentration of these sarcoplasmic enzymes in serum is elevated, presumably because the diseases affect the integrity of surface membranes of the muscle, allowing the enzymes to leak into the bloodstream. The enzyme activity most commonly used for diagnosing myopathy is creatine kinase, an enzyme that phosphorylates creatine and is important in the energy metabolism of muscle.

Muscle histochemical appearance in a biopsy can also provide a useful diagnostic tool. Human muscle fibers are identified by histochemical reactions as type I or type II, which respectively are either aerobic (enriched for oxidative enzymes) or anaerobic (abundant glycolytic enzymes) (Chapter 31). All muscle fibers innervated by a single motor neuron are of the same histochemical type. However, the muscle fibers of one motor unit are normally interspersed among the muscle fibers of other motor units. In a cross section of healthy muscle, enzyme stains show that oxidative or glycolytic fibers are intermixed in a "checkerboard" pattern.

In chronic neurogenic diseases, the muscle innervated by a dying motor neuron becomes atrophic and some muscle fibers disappear. Axons of surviving neurons tend to sprout and reinnervate some of the adjacent remaining muscle fibers. Because the motor neuron determines the biochemical and thus histochemical properties of a muscle fiber, the reinnervated muscle fibers assume the histochemical properties of the innervating neuron. As a result, the fibers of a muscle in neurogenic disease become clustered by type (a pattern called fiber-type grouping).

If the disease is progressive and the neurons in the surviving motor units also become affected, atrophy occurs in groups of adjacent muscle fibers belonging to the same histochemical type, a process called group atrophy. In contrast, in myopathic diseases, the muscle fibers are affected in a more or less random fashion. Sometimes an inflammatory cellular response is evident, and sometimes there is prominent infiltration of the muscle by fat and connective tissue.

Fasciculations—visible twitches of muscle that can be seen as flickers under the skin—are often signs of neurogenic diseases. They result from involuntary but synchronous contractions of all muscle fibers in a motor unit. Fibrillations—spontaneous contractions within single muscle fibers—can also be signs of ongoing denervation of muscle. Fibrillations are not visible but can be recorded with an EMG. The electrical record of a fibrillation is a low-amplitude potential that reflects electrical activity in a single muscle cell. Electrophysiological studies suggest that fasciculations arise in the motor nerve terminal.

In diagnosing motor neuron disorders, clinicians have historically distinguished between so-called lower motor neurons and premotor neurons. Lower motor neurons are motor neurons of the spinal cord and brain stem that directly innervate skeletal muscles. Premotor neurons, also known as "upper" motor neurons, originate in the motor cortex and issue commands for movements to the lower motor neurons through their axons in the corticospinal (pyramidal) tract.

Diseases of upper motor neurons can be distinguished from those affecting lower motor neurons by distinct sets of symptoms. Disorders of lower motor neurons cause atrophy, fasciculations, decreased muscle tone, and loss of tendon reflexes, whereas disorders of upper motor neurons and their axons result in spasticity, overactive tendon reflexes, and abnormal plantar extensor reflex (the Babinski sign).

The primary symptom of disorders of the neuromuscular junction is weakness; in some neuromuscular junction diseases, this weakness is quite variable even over the course of a single day.

A Variety of Diseases Target Motor Neurons and Peripheral Nerves

Motor Neuron Diseases Do Not Affect Sensory Neurons (Amyotrophic Lateral Sclerosis)

The best-known disorder of motor neurons is amyotrophic lateral sclerosis (ALS; Lou Gehrig disease). "Amyotrophy" is another term for neurogenic atrophy of muscle; "lateral sclerosis" refers to the hardness felt when the pathologist examines the spinal cord at autopsy. This hardness results from the proliferation of astrocytes and scarring of the lateral columns of the spinal cord due to degeneration of the corticospinal tracts.

The symptoms of ALS usually start with painless weakness in a single arm or leg. Typically, the patient, often a man in his 40s or 50s, discovers that he has trouble in executing fine movements of the hands—typing, playing the piano, playing baseball, fingering coins, or working with tools. This focal weakness then spreads over 3 or 4 years to involve all four limbs, as well as the muscles of chewing, speaking, swallowing, and breathing.

Most cases of ALS involve both the upper and the lower motor neurons. Some motor neurons are spared, notably those supplying ocular muscles and those involved in voluntary control of bladder sphincters. The typical weakness of the hand is associated with wasting of the small muscles of the hands and feet and fasciculations of the muscles of the forearm and upper arm. These signs of lower motor neuron disease are often associated with hyperreflexia, an over-responsiveness in tendon reflexes characteristic of corticospinal upper motor neuron disease. The cause of most cases (90%) of ALS is not known; the disease is progressive and ultimately affects the muscles of respiration. There is no effective treatment for this fatal condition.

About 10% of cases are inherited in a dominant manner (Table 57–2). In North America, greater than 25% of inherited cases arise from mutations in the gene *C9orf72*. The offending genetic defect is an expansion in an intronic hexanucleotide repeat, from 30 or fewer in normal individuals to hundreds or even thousands in affected individuals. Besides giving rise to conventional ALS, mutations in *C9orf72* can also cause frontotemporal dementia. The toxicity of the mutant C9orf72 protein probably reflects both a reduction in total activity of the mutant protein and toxic effects of the intronic expansion. For example, the expanded intronic segments produce intranuclear deposits of RNA that likely sequester and inactivate important nuclear proteins. In addition, the expanded RNA is translated to

Table 57–2 Selected Amyotrophic Lateral Sclerosis Genes

				Proportion of ALS	
Gene	**Protein**	**Protein function**	**Mutations**	**Familial**	**Sporadic**
SOD1	Cu-Zn superoxide dismutase	Superoxide dismutase	>150	20%	2%
DCTN1	Dynactin subunit 1	Component of dynein motor complex	10	1%	<1%
ANG	Angiogenin	Ribonuclease	>10	<1%	<1%
TARDBP	TDP-43	RNA-binding protein	>40	5%	<1%
FUS	FUS	RNA-binding protein	>40	5%	<1%
VCP	Transitional endoplasmic reticulum ATPase	Ubiquitin segregase	5	1–2%	<1%
OPTN	Optineurin	Autophagy adaptor	1	4%	<1%
C9orf72	C9orf72	Possible guanine nucleotide exchange factor	Intronic GGGGCC	25%	10%
UBQLN2	Ubiquilin 2	Autophagy adaptor	5	<1%	<1%
SQSTM1	Sequestosome 1	Autophagy adaptor	10	<1%	?
FFN1	Profilin-1	Actin-binding protein	5	<1%	<1%
HNRNPA1	hnRNP A1	RNA-binding protein	3	<1%	<1%
MATR3	Matrin 3	RNA-binding protein	4	<1%	<1%
TUBA4A	Tubulin α-4A chain	Microtubule subunit	7	<1%	<1%
CHCHD10	Coiled-coil-helix-coiled-coil-helix domain-containing protein 10	Mitochondrial protein of unknown function	2	<1%	<1%
TBK1	Serine/threonine-protein kinase TBK1	Regulates autophagy and inflammation	10	1%	<1%

Source: Modified from Taylor, Brown, and Cleveland 2016.

produce peptides composed of repeated couplets of amino acids, such as poly-(glycine-proline) or poly-(proline-arginine); some of these are neurotoxic.

Two other genes commonly mutated in ALS are *SOD1* and *TDP43*. *SOD1* encodes the protein copper/zinc cytosolic superoxide dismutase, whereas *TDP43* encodes a 43-kD, RNA-interacting protein that is normally intranuclear but is mislocalized to the cytosol in most cases of ALS (both inherited and sporadic). Mutations in *SOD1* and several other ALS genes (eg, *ubiquilin-2*) destabilize the conformation of the protein product, promoting misfolding and causing adverse consequences to diverse subcellular processes and compartments. By contrast, mutations in *TDP43* and a few other ALS genes (eg, *FUS*) encoding RNA binding proteins act at the RNA level, impairing RNA homeostasis and perturbing critical processes such as surveillance of gene splicing. Infrequently, familial ALS is caused by mutations in genes encoding cytoskeletal proteins such as profilin-1, dynactin, or tubulin-A4.

Many studies suggest that mutant ALS-associated proteins tend to aggregate, particularly in membraneless organelles called stress granules that form in conditions of cellular distress. Several lines of investigation support the view that aggregates migrate and transmit pathology between adjacent cells, accounting for spread of the disease to different brain regions. Strikingly, mice that express high levels of defective SOD1 or profilin-1 proteins develop a lethal, adult-onset form of motor neuron disease, but mice expressing equivalently high levels of normal SOD1 or profilin-1 proteins do not. These findings are consistent with the concept that the defective protein has gained some sort of toxic function.

In the past 10 years, it has also become clear that motor neuron pathophysiology is modulated by the reactions of nonneural cells to degeneration in the motor neuron. Thus, in most cases of ALS, there are varying degrees of proliferation and activation of microglia, astrocytes, and some populations of lymphocytes, which may begin as compensatory responses but can eventually adversely affect the injured motor neurons. Genetic studies have underscored the importance of non–cell-autonomous factors, such as variants that reduce function of the microglial gene *TREM-2* and enhance the risk of developing not only ALS but also other neurodegenerative disorders (eg, Alzheimer disease).

Progressive bulbar palsy is a type of motor neuron disease in which damage is restricted to muscles innervated by cranial nerves, causing dysarthria (difficulty speaking) and dysphagia (difficulty swallowing). (The term "bulb" is used interchangeably with "pons," the structure at the base of the brain where motor neurons that innervate the face and swallowing muscles reside, and "palsy" means weakness). If only lower motor neurons are involved, the syndrome is called progressive spinal muscular atrophy.

Progressive spinal muscular atrophy is actually a developmental motor neuron disorder characterized by weakness, wasting, loss of reflexes, and fasciculations. Most cases arise in infancy and are caused by recessively inherited mutations in the gene encoding a protein called survival motor neuron (SMN). Survival in these cases is very short, although there are rare cases that begin in late childhood or even early adulthood and are associated with longer survival of many years. The SMN protein is implicated in trafficking RNA in and out of the nucleus and in the formation of complexes that are important in RNA splicing. The SMN locus on chromosome 5 in humans has two almost identical copies of the *SMN* gene: *SMN1* produces a full-length SMN protein, while alternative splicing of *SMN2* causes omission of the seventh exon in the gene, leading to expression of a small amount of full-length SMN and a shortened SMN. The clinical effect of the loss of full-length SMN from mutations at the main locus can be mitigated to some degree by the shortened SMN protein expressed by the *SMN2* gene (Figure 57–4A,B).

Two treatment strategies have achieved extraordinary benefits in spinal muscular atrophy. In one, small strings of approximately 20 nucleic acids (antisense oligonucleotides [ASO]s) are administered to alter splicing of the *SMN2* gene so that it produces higher levels of the full-length SMN protein (Figure 57-4A). This occurs because the ASO is targeted to bind to the SMN2 RNA and inhibit the action of the RNA binding protein hnRNPA1/A2 that normally leads the splicing machinery to skip exon 7. By blocking the binding of hnRNPA1/A2, the ASO blocks the inhibitory effect of hnRNPA1/A2 on splicing, promoting expression of full-length SMN protein (Figure 57–4B). It seems likely that ASOs will become powerful therapeutic tools with many applications. In this example, ASO is used to promote exon inclusion; as noted below in the discussion on muscle dystrophy, ASO can also be used to promote exon skipping. It can also be used in other paradigms to inhibit or enhance levels of target gene expression.

The second approach to treating spinal muscular atrophy has been to deliver the missing *SMN* gene to spinal motor neurons and muscle using high doses of intravenously infused adeno-associated virus carrying the *SMN1* gene. This, too, dramatically augments survival in infantile spinal muscular atrophy (Figure 57–4B).

ALS and its variants are restricted to motor neurons; they do not affect sensory neurons or autonomic neurons. The acute viral disease poliomyelitis is also confined to motor neurons. These diseases illustrate the individuality of nerve cells and the principle of selective vulnerability. The basis of this selectivity is, in general, not understood.

Diseases of Peripheral Nerves Affect Conduction of the Action Potential

Diseases of peripheral nerves may affect either axons or myelin. Because motor and sensory axons are bundled together in the same peripheral nerves, disorders of peripheral nerves usually affect both motor and sensory functions. Some patients with peripheral neuropathy report abnormal, frequently unpleasant, sensory experiences such as numbness, pins-and-needles prickling, or tingling. When these sensations occur spontaneously without an external sensory stimulus, they are called paresthesias.

Patients with paresthesias usually have impaired perception of cutaneous sensations (pain and temperature), often because the small fibers that carry these sensations are selectively affected. This is not always the case, however. Proprioceptive sensations (position and vibration) can be lost without loss of cutaneous sensation. Lack of pain perception may lead to injuries. The sensory deficits are more prominent distally (called a glove-and-stocking pattern), likely because the distal portions of the nerves are most remote from the cell body and therefore most susceptible to disorders that interfere with axonal transport of essential metabolites and proteins.

Peripheral neuropathy is first manifested by weakness that is usually distal. Tendon reflexes are usually