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

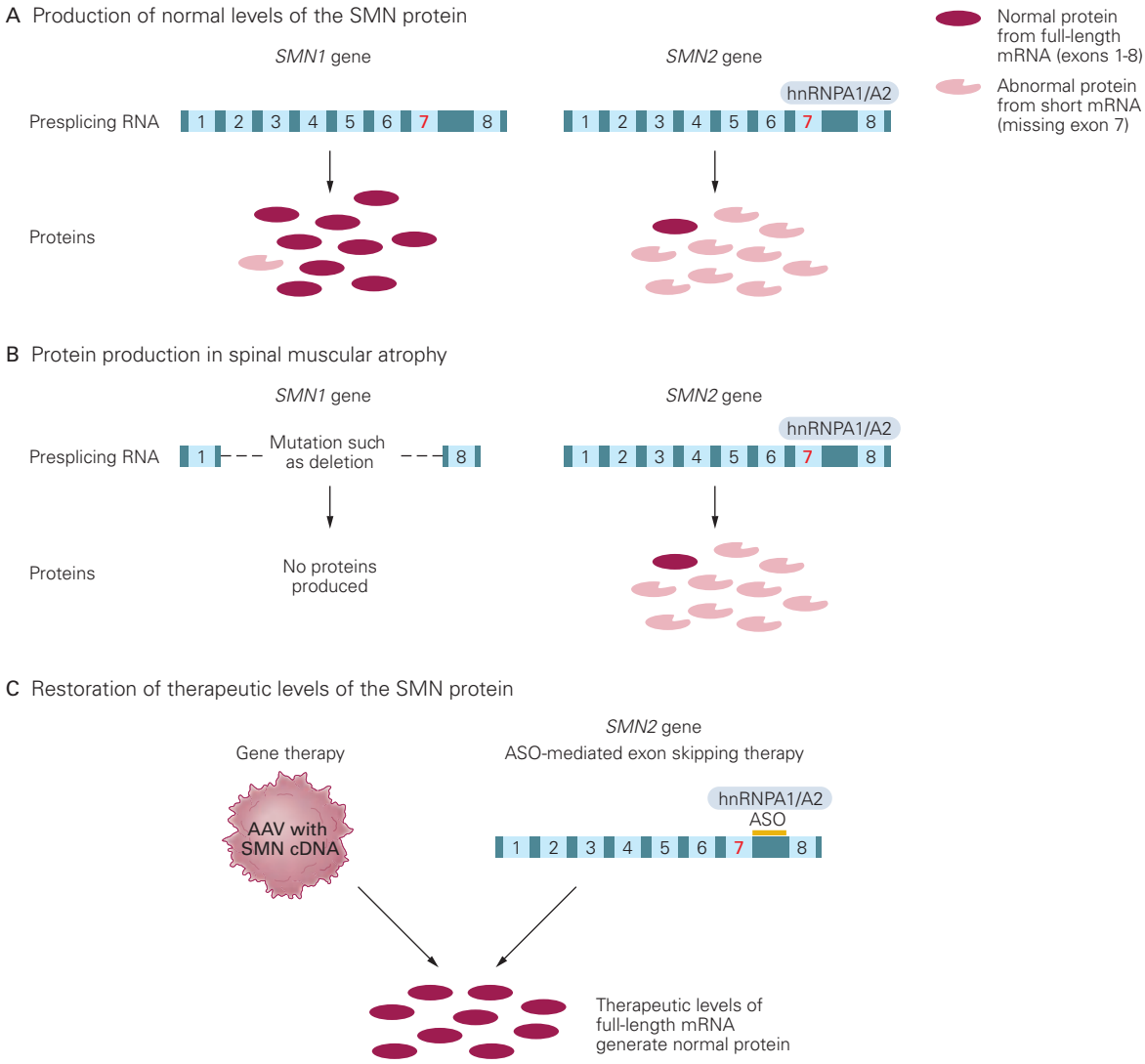

Figure 57–4 Spinal motor atrophy caused by defective survival motor neuron gene (*SMN1*) can be treated by gene replacement therapy or by manipulating splicing of *SMN2*.

A. Normally, most of the survival motor neuron (**SMN**) protein is produced from the *SMN1* gene, whose mRNA is spliced from eight exons. In normal circumstances, about 90% of the mRNA has all eight exons, yielding normal levels of the SMN protein. In the adjacent sister gene, *SMN2*, binding of the protein hnRNPA1/A2 to the *SMN2* transcript excludes exon 7; *SMN2* therefore makes a shortened SMN protein.

B. In spinal muscular atrophy, genetic lesions (commonly deletions) in *SMN1* lead to a marked reduction in levels of total SMN protein.

C. When SMN1 protein is absent, one therapeutic approach is to replace the missing *SMN1* gene using an adeno-associated viral vector (**AAV**) to deliver the missing gene to the central nervous system and muscle. An alternative approach is to deliver an antisense oligonucleotide (**ASO**) that blocks the effect of hnRNPA1/A2, thereby enhancing production of a full-length mRNA (with all eight exons) from *SMN2*. This restores SMN protein levels.

depressed or lost, fasciculation is seen only rarely, and wasting does not ensue unless the weakness has been present for many weeks.

Neuropathies may be either acute or chronic. The best-known acute neuropathy is Guillain-Barré syndrome. Most cases follow respiratory infection or infectious diarrhea, but the syndrome may occur without apparent preceding illness. The condition may be mild or so severe that mechanical ventilation is required. Cranial nerves may be affected, leading to paralysis of ocular, facial, and oropharyngeal muscles. The disorder is attributed to an autoimmune attack on peripheral nerves by circulating antibodies. It is therefore treated by removing the offending antibodies by

infusions of gamma globulin and plasmapheresis (a procedure in which blood is removed from a patient, cells are separated from the antibody-carrying plasma, and the cells alone are returned to the patient).

The chronic neuropathies vary from mild to incapacitating or even fatal conditions. There are many varieties, including genetic diseases (acute intermittent porphyria, Charcot-Marie-Tooth disease), metabolic disorders (diabetes, vitamin B_{12} deficiency), toxicities (lead), nutritional disorders (alcoholism, thiamine deficiency), carcinomas (especially carcinoma of the lung), and immunological disorders (plasma cell diseases, amyloidosis). Some chronic disorders, such as neuropathy due to vitamin B_{12} deficiency in pernicious anemia, are amenable to therapy.

In addition to being acute or chronic, neuropathies may be categorized as demyelinating (in which the myelin sheath breaks down) or axonal (in which the axon is affected). In demyelinating neuropathies, as might be expected from the role of the myelin sheath in saltatory conduction, conduction velocity is slowed. In axonal neuropathies, the myelin sheath is not affected and conduction velocity is normal.

Axonal and demyelinating neuropathies may lead to positive or negative symptoms and signs. The negative signs consist of weakness or paralysis, loss of tendon reflexes, and impaired sensation resulting from loss of motor and sensory nerves. The positive symptoms of peripheral neuropathies consist of paresthesias that arise from abnormal impulse activity in sensory fibers and either spontaneous activity of injured nerve fibers or electrical interaction (cross-talk) between abnormal axons, a process called ephaptic transmission to distinguish it from normal synaptic transmission. It is not known why damaged nerves become hyperexcitable. Even lightly tapping the site of injury can evoke a burst of painful sensations in the region over which the nerve is distributed.

Negative symptoms, which have been studied more thoroughly than positive symptoms, can be attributed to three basic mechanisms: conduction block, slowed conduction, and impaired ability to conduct impulses at higher frequencies. Conduction block was first recognized in 1876 when the German neurologist Wilhelm Erb observed that stimulation of an injured peripheral nerve below the site of injury evoked a muscle response, whereas stimulation above the site of injury produced no response. He deduced that the lesion blocked conduction of impulses of central origin, even when the segment of the nerve distal to the lesion was still functional. Later studies confirmed this conclusion by showing that selective application of diphtheria and other toxins produces conduction block by causing demyelination only at the site of application (Figure 57–5).

Why does demyelination produce nerve block, and how does it lead to slowing of conduction velocity? Conduction velocity is much more rapid in myelinated fibers than in unmyelinated axons for two reasons (Chapter 9). First, there is a direct relationship between conduction velocity and axon diameter, and myelinated axons tend to be larger in diameter. Second, membrane capacitance in the myelinated regions of the axon is lower than at the unmyelinated nodes of Ranvier, greatly speeding up the rate of depolarization and thus conduction. With demyelination, the spatial distribution of ion channels along the denuded axon is not optimal for supporting action potential propagation and may even cause a failure of conduction. When myelin is disrupted by disease, the action potentials in different axons of a nerve begin to conduct at slightly different velocities. As a result, the nerve loses its normal synchrony of conduction in response to a single stimulus. (Figure 57–2 shows how conduction velocities are measured in peripheral nerves.)

This slowing and loss of synchrony are thought to account for some of the early clinical signs of demyelinating neuropathy. For example, functions that normally depend on the arrival of synchronous bursts of neural activity, such as tendon reflexes and vibratory sensation, are lost soon after the onset of a chronic neuropathy. As demyelination becomes more severe, conduction becomes blocked. This block may be intermittent, occurring only at high frequencies of neural firing, or complete (Figure 57–3).

The Molecular Basis of Some Inherited Peripheral Neuropathies Has Been Defined

Myelin proteins are affected in a group of demyelinating hereditary peripheral neuropathies collectively termed Charcot-Marie-Tooth (CMT) disease. CMT is characterized by muscle weakness and wasting, loss of reflexes, and loss of sensation in the distal parts of the limbs. These symptoms appear in childhood or adolescence and are slowly progressive.

One form (type 1) has the features of a demyelinating neuropathy (Figure 57–5). Conduction in peripheral nerves is slow, with histological evidence of demyelination followed by remyelination. Sometimes, the remyelination leads to gross hypertrophy of the nerves. Type 1 disorders are inexorably progressive, without remissions or exacerbations. Another form (type 2) has normal nerve conduction velocity and is considered an axonal neuropathy without demyelination. Both types 1 and 2 are inherited as autosomal dominant diseases.

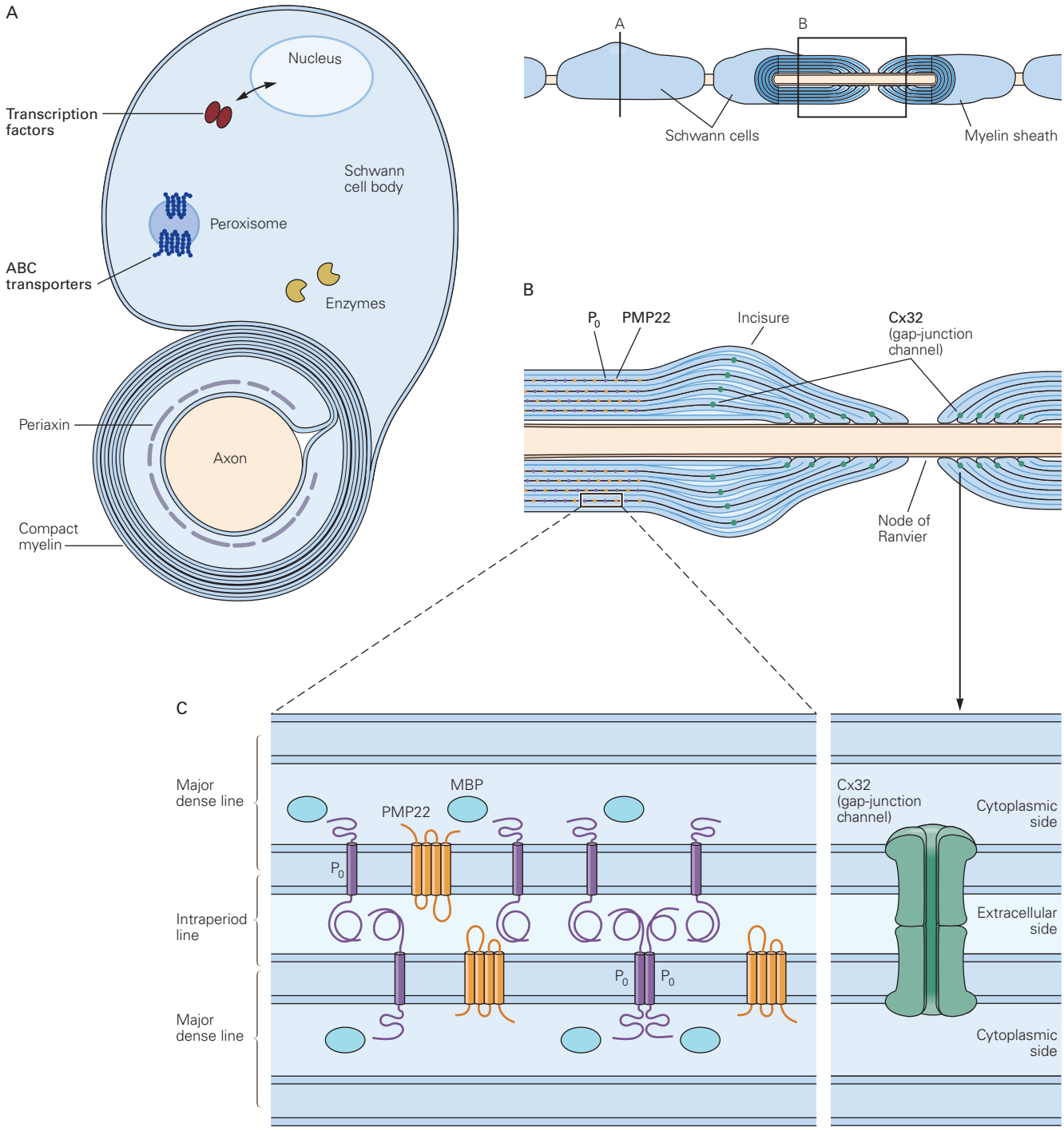

Figure 57–5 Gene defects in components of myelin cause demyelinating neuropathies.

A. Myelin production and function in the Schwann cell can be adversely affected by many genetic defects, including abnormalities in transcription factors, **ABC** (ATP-binding cassette) transporters in peroxisomes, and multiple proteins implicated in organizing myelin. Viewed microscopically at high power, the site of apposition of the intracellular faces of the Schwann cell membrane appears as a dense line, whereas the apposed extracellular faces are described as the "intraperiod line" (see part **C**). (Adapted from Lupski 1998.)

B. Peripheral axons are wrapped in multiple layers of thin sheaths of myelin that are processes of Schwann cells. The myelin is compact and tight except near the nodes of Ranvier and at focal sites described as "incisures" by Schmidt and Lanterman. Three myelin-associated proteins are defective in three different demyelinating neuropathies: P_0 (Dejerine-Sottas infantile neuropathy), peripheral myelin protein (**PMP22**) (Charcot-Marie-Tooth neuropathy type 1), and connexin-32 (**Cx32**) (X-linked Charcot-Marie-Tooth neuropathy). (Adapted from Lupski 1998.)

C. The rim of cytoplasm in which myelin basic protein (**MBP**) is located defines the major dense line, whereas the thin layer of residual extracellular space defines the intraperiod line. Mutations in PMP22 and P_0 genes adversely affect the organization of compact myelin. (Adapted, with permission, from Brown and Amato 2002.)

Type 1 disease is attributed to mutations on two different chromosomes (locus heterogeneity). The more common form (type 1A) is linked to chromosome 17, while the less common form (1B) is localized to chromosome 1. The genes at these loci have been directly implicated in myelin physiology (Figure 57–5). Type 1A involves a defect in peripheral myelin protein 22, and type 1B the myelin protein P_0. Moreover, an X-linked form of demyelinating neuropathy occurs because of mutations in the gene expressing connexin-32, a subunit of the gap-junction channels that interconnect myelin folds near the nodes of Ranvier (Figure 57–5B,C). Still other genes have been implicated in inherited demyelination.

Some of the genes and proteins implicated in axonal neuropathies are shown in Figure 57–6 and Table 57–3. Genes encoding the neurofilament light subunit and an axonal motor protein related to kinesin, which is important for transport along microtubules, are mutated in two types of axonal neuropathies. Defects in these genes are associated with peripheral neuropathies with prominent weakness. The mechanisms by which genes alter axonal function in other axonal neuropathies are less evident.

As noted above, a wide range of problems other than genetic mutations lead to peripheral neuropathies. Particularly striking are nerve defects associated with the presence of autoantibodies directed against ion channels in distal peripheral nerves. For example, some individuals with motor unit instability (cramps and fasciculations), as well as sustained or exaggerated muscle contractions caused by hyperexcitability of motor nerves, have serum antibodies directed against one or more axonal voltage-gated K^+ channels. The prevailing view is that binding of the autoantibodies to the channels reduces K^+ conductance and thereby depolarizes the axon, leading to augmented and sustained firing of the distal motor nerve and associated muscle contractions. Alterations in ion channel function underlie a variety of neurological disorders, as in acquired disorders of channels in the neuromuscular junction and inherited defects in voltage-gated channels in muscle (discussed below).

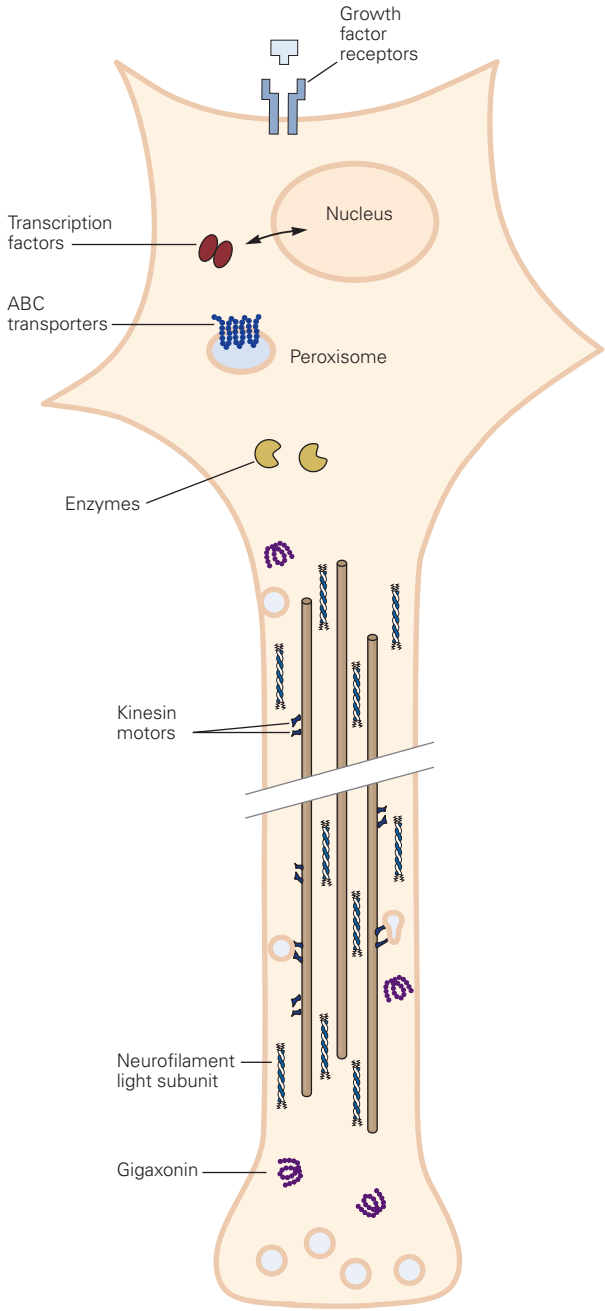

Figure 57–6 Gene defects that cause axonal neuropathies. These include defects in receptors for growth factors, ABC (ATP-binding cassette) transporters in peroxisomes, cytosolic enzymes, microtubule motor proteins like the kinesins, neurofilament proteins, and other structural proteins such as gigaxonin. (Adapted, with permission, from Brown and Amato 2002.)

Disorders of Synaptic Transmission at the Neuromuscular Junction Have Multiple Causes

Many diseases involve disruption of chemical transmission between neurons and their target cells. By analyzing such abnormalities, researchers have learned a great deal about the mechanisms underlying normal synaptic transmission as well as disorders caused by dysfunction at the synapse.

Table 57–3 Representative Peripheral Neuropathy Genes

Site of primary defect	Protein	Disease
Myelin	Proteolipid myelin protein 22	Charcot-Marie-Tooth disease (CMT)
	Proteolipid protein P_0	Infantile CMT (Dejerine-Sottas neuropathy)
	Connexin-32	X-linked CMT
Axon	Kinesin KIF1Bβ motor protein	Motor predominant neuropathy
	Heat shock protein 27	Motor predominant neuropathy
	Neurofilament light subunit	Motor predominant neuropathy
	Tyrosine kinase A receptor	Congenital sensory neuropathy
	ABC1 transporter	Tangier disease
	Transthyretin	Amyloid neuropathy

Diseases that disrupt transmission at the neuromuscular junction fall into two broad categories: those that affect the presynaptic terminal and those that primarily involve the postsynaptic membrane. In both categories, the most intensively studied cases are autoimmune and inherited defects in critical synaptic proteins.

Myasthenia Gravis Is the Best-Studied Example of a Neuromuscular Junction Disease

The most common and extensively studied disease affecting synaptic transmission is myasthenia gravis, a disorder at the neuromuscular junction in skeletal muscle. Myasthenia gravis (the term means severe weakness of muscle) has two major forms. The most prevalent is the autoimmune form. The second is congenital and heritable; it is not an autoimmune disorder and is heterogeneous. Fewer than 500 of these congenital cases have been identified, but they have provided information about the organization and function of the human neuromuscular junction. This form is discussed later in the chapter.

In autoimmune myasthenia gravis, antibodies are produced against components of the postsynaptic end-plate in muscle, such as the nicotinic acetylcholine (ACh) receptor and muscle-specific tyrosine kinase (MuSK). Anti–ACh receptor antibodies interfere with synaptic transmission by reducing the number of functional receptors or by impeding the interaction of ACh with its receptors. As a result, communication between the motor neuron and the skeletal muscle becomes weakened. This weakness always affects cranial muscles—eyelids, eye muscles, and oropharyngeal muscles—as well as limb muscles. Its severity of symptoms varies over the course of a single day, from day to day, or over longer periods (giving rise to periods of remission or exacerbation), making myasthenia gravis unlike most other diseases of muscle or nerve. The weakness is reversed by drugs that inhibit acetylcholinesterase, the enzyme that degrades ACh. As one example, when patients are asked to look upward in a sustained gaze, the eyelids tire after several seconds and droop downward (ptosis). Like decremental responses on EMG, this fatiguability and drooping reverse after treatment with inhibitors of acetylcholinesterase (Figure 57–7).

When a motor nerve is stimulated at rates of two to five stimuli per second, the amplitude of the compound

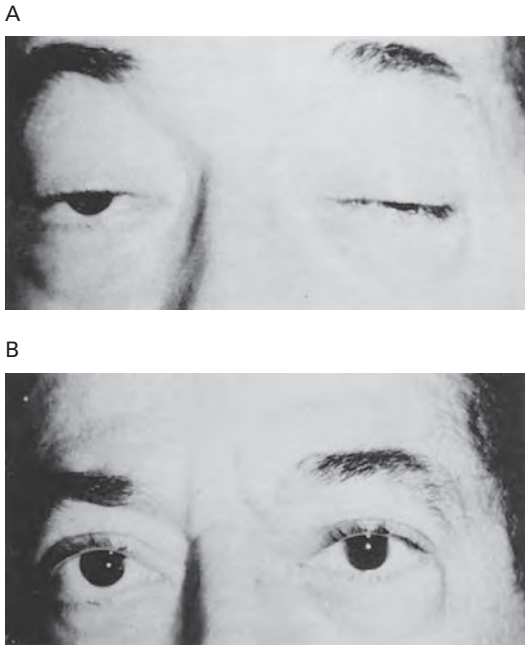

Figure 57–7 Myasthenia gravis often selectively affects the cranial muscles. (Reproduced, with permission, from Rowland, Hoefer, and Aranow 1960.)

A. Severe drooping of the eyelids, or ptosis, is characteristic of myasthenia gravis. This patient also could not move his eyes to look to either side.

B. One minute after an intravenous injection of 10 mg of edrophonium, an inhibitor of acetylcholinesterase, both eyes are open and can be moved freely.

action potential evoked in normal human muscle remains constant. In myasthenia gravis, the amplitude of the evoked compound action potential decreases rapidly. This pattern of decremental response of the compound muscle action potential to repetitive stimulation of the motor nerve mirrors the clinical symptom of fatiguability in myasthenia. Moreover, this abnormality resembles the pattern induced in normal muscle by d-tubocurarine (the active compound in curare), which blocks nicotinic ACh receptors and inhibits the action of ACh at the neuromuscular junction. Neostigmine (Prostigmin), which inhibits acetylcholinesterase and thus increases the duration of action of ACh at the neuromuscular junction, reverses the decrease in amplitude of evoked compound action potentials in myasthenic patients (Figure 57–8).

About 15% of adult patients with myasthenia have benign tumors of the thymus (thymomas). As the symptoms in myasthenic patients are often improved by removal of these tumors, some element of the thymoma may stimulate autoimmune pathology. Indeed, myasthenia gravis often affects people who have other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, or Graves disease (hyperthyroidism).

Normally, an action potential in a motor axon releases enough ACh from synaptic vesicles to induce a large excitatory end-plate potential with an amplitude of about 70 to 80 mV relative to the resting potential of –90 mV (Chapter 12). Thus, the normal end-plate potential is greater than the threshold needed to initiate an action potential, about –45 mV. In normal muscle, the difference between the threshold and the actual end-plate potential amplitude—the safety factor—is therefore quite large (Figure 57–8). In fact, in many muscles, the amount of ACh released during synaptic transmission can be reduced to as little as 25% of normal before it fails to initiate an action potential.

The density of ACh receptors is reduced over time in myasthenia. This reduces the probability that a molecule of ACh will find a receptor before it is hydrolyzed by the acetylcholinesterase. In addition, the geometry of the end-plate is also disturbed in myasthenia (Figure 57–9). The normal infolding at the junctional folds is reduced and the synaptic cleft is enlarged. These morphological changes increase the diffusion of

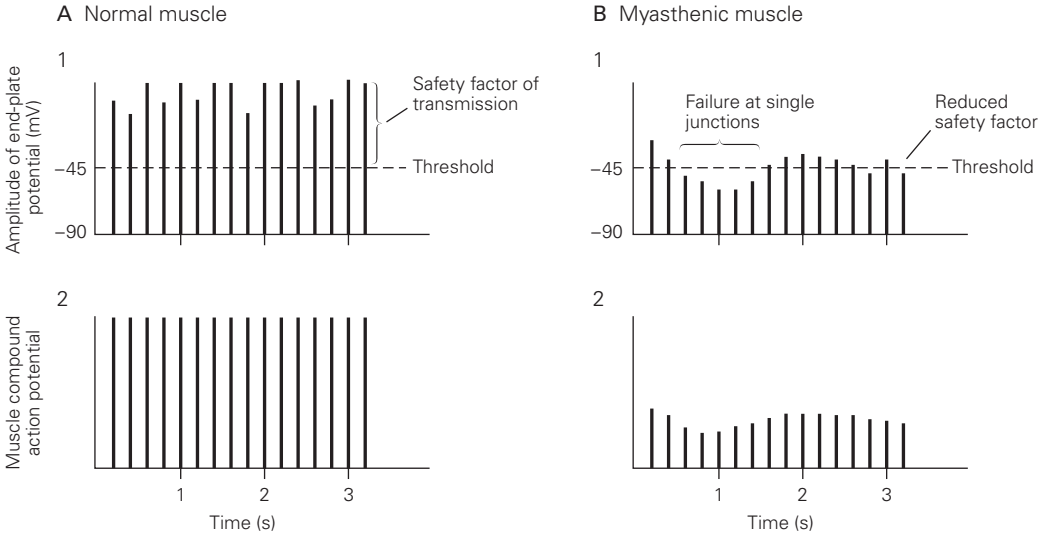

Figure 57–8 Synaptic transmission at the neuromuscular junction fails in myasthenia gravis. (Reproduced, with permission, from Lisak and Barchi 1982.)

A. In the normal neuromuscular junction, the amplitude of the end-plate potential is so large that all fluctuations in the efficiency of transmitter release occur well above the threshold for a muscle action potential. This results in a large safety factor for synaptic transmission (**1**). Therefore, during repetitive stimulation of the motor nerve, the amplitude of the compound action potentials, representing the contributions from all muscle fibers in which synaptic transmission is successful in triggering an action potential, is constant and invariant (**2**).

B. In the myasthenic neuromuscular junction, postsynaptic changes reduce the amplitude of the end-plate potential so that under optimal circumstances the end-plate potential may be just sufficient to produce a muscle action potential. Fluctuations in transmitter release that normally accompany repeated stimulation now cause the end-plate potential to drop below this threshold, leading to conduction failure at that junction (**1**). The amplitude of the compound action potentials in the muscle declines progressively and shows only a small and variable recovery (**2**).

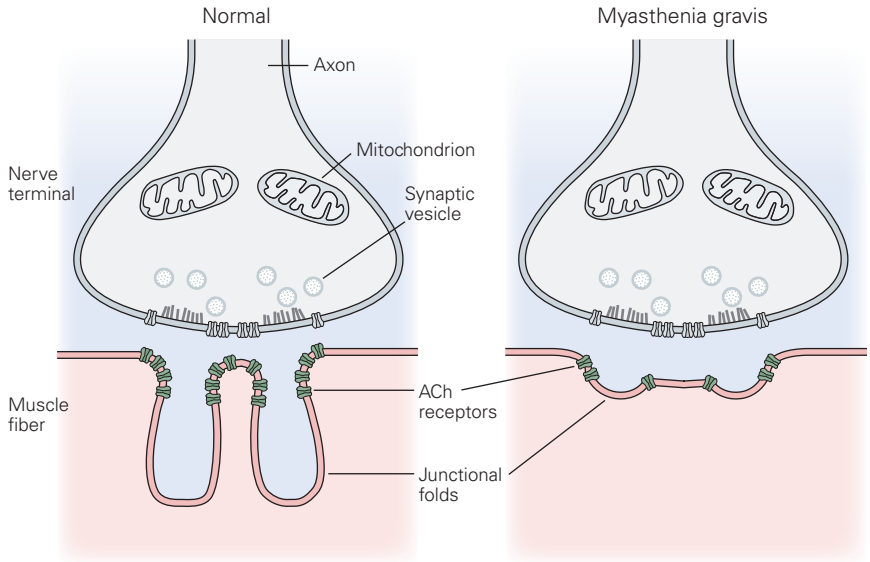

Figure 57–9 Morphological abnormalities of the neuromuscular junction are characteristic of myasthenia gravis. At the neuromuscular junction, acetylcholine (**ACh**) is released by exocytosis of synaptic vesicles at active zones in the nerve terminal. Acetylcholine flows across the synaptic cleft to reach ACh receptors that are concentrated at the peaks of junctional folds. Acetylcholinesterase in the cleft rapidly terminates transmission by hydrolyzing ACh. The myasthenic junction has reduced numbers of ACh receptors, simplified synaptic folds, a widened synaptic space, but a normal nerve terminal.

ACh away from the synaptic cleft and further reduce the probability of ACh interacting with the few remaining functional receptors. As a result, the amplitude of the end-plate potential is reduced to the point where it is barely above threshold (Figure 57–8).

Thus, in myasthenia, synaptic transmission is readily blocked even though the vesicles in the presynaptic terminals contain normal amounts of ACh and the process of transmitter release is intact. Both the physiological abnormality (the decremental response) and the clinical symptoms (muscle weakness) are partially reversed by drugs that inhibit acetylcholinesterase. This is because the released ACh molecules remain unhydrolyzed for a longer time, and this increases the probability that they will interact with receptors.

How do antibodies cause the symptoms of myasthenia? The antibodies do not simply occupy the ACh binding site. Rather, they appear to react with epitopes elsewhere on the receptor molecule. This increases the turnover of nicotinic ACh receptors, probably because myasthenic antibodies bind and cross-link the receptors, triggering their degradation (Figure 57–9). In addition, some myasthenic antibodies bind proteins of the complement cascade of the immune system, causing lysis of the postsynaptic membrane.

Despite the evidence documenting the primary role of antibodies against the nicotinic ACh receptor in myasthenia, about one-fifth of patients with myasthenia do not have these antibodies—including some who respond to anti-immune therapy like plasmapheresis. Instead, the majority of these patients have antibodies to other postsynaptic proteins, such as MuSK (*mu*scle-specific trk-related receptor with a *K*ringle domain) and lipoprotein-related protein 4 (LPR4), which is an activator of MuSK. MuSK is a muscle-specific receptor tyrosine kinase that interacts with another postsynaptic protein, agrin, to organize the nicotinic ACh receptors into clusters at the neuromuscular junction (Chapter 48); it appears to be functionally important both during development and in the adult. The anti-MuSK antibodies block some of the normal clustering of the nicotinic ACh receptors following the interaction of agrin with MuSK. Anti-LPR4 antibodies also block ACh receptor clustering.

Treatment of Myasthenia Is Based on the Physiological Effects and Autoimmune Pathogenesis of the Disease

Anticholinesterases, especially pyridostigmine, provide some symptomatic relief but do not alter the basic disease. Immunosuppressive therapies such as corticosteroids and azathioprine or related drugs suppress antibody synthesis. Intravenous infusions of pooled immunoglobulins reduce levels of the pathogenic autoantibodies and ameliorate symptoms, often within a few days. An analogous benefit is achieved by plasmapheresis, which involves filtering the plasma. Although the benefit of these interventions is short-lived, it may be sufficient to prepare a patient for thymectomy or to support the patient through more severe episodes.

There Are Two Distinct Congenital Forms of Myasthenia Gravis

In two distinct types of myasthenia, symptoms may be present from birth or shortly thereafter. In neonatal

myasthenia, the mother herself has autoimmune myasthenia that is transmitted passively to the newborn via the immune system. In congenital myasthenia, the infant has an inherited defect in some component of the neuromuscular junction, rather than an autoimmune disease, and thus does not have serum antibodies to the nicotinic ACh receptor or MuSK.

Congenital myasthenic syndromes fall into three broad groups based on the site of the defect in the neuromuscular synapse: presynaptic, synaptic cleft, and postsynaptic forms. Clinical features common to all three types include a positive family history, weakness with easy fatigability (present since infancy), drooping of the eyelids (ptosis), a decremental response to repetitive stimulation on EMG, and negative screening for anti-nicotinic ACh receptor antibodies. Subnormal development of the skeletal muscles reflects the fact that normal function at the neuromuscular synapse is required to maintain normal muscle bulk.

In one presynaptic form of congenital myasthenia, the enzyme choline acetyltransferase is absent or reduced in the distal motor terminal. This enzyme is essential for the synthesis of ACh from choline and acetyl-CoA (Chapter 16). In its absence, the synthesis of ACh is impaired. The result is weakness that usually begins in infancy or early childhood. In another presynaptic form of congenital myasthenia, the number of quanta of ACh released after an action potential is less than normal; the molecular basis for this defect is not known.

Congenital myasthenia may also result from the absence of acetylcholinesterase in the synaptic cleft. In this circumstance, end-plate potentials and miniature end-plate potentials are not small, as in autoimmune myasthenia, but are markedly prolonged, which may explain the repetitive response of the evoked muscle potential in those patients. Cytochemical studies indicate that ACh-esterase is absent from the basement membranes. At the same time, nicotinic ACh receptors are preserved.

The physiological consequence of ACh-esterase deficiency is sustained action of ACh on the end-plate and ultimately the development of an end-plate myopathy. This myopathy indicates that skeletal muscle can react adversely to excessive stimulation at the neuromuscular junction. In treating this disorder, it is critical to avoid using agents that inhibit ACh-esterase, which can increase the electrical firing at the end-plate and thereby exacerbate the muscle weakness.

The majority of congenital myasthenia cases are caused by primary mutations in the genes encoding different subunits of the ACh receptor. The *slow channel syndrome* is characterized by prominent limb weakness but little weakness of cranial muscles (the reverse of the pattern usually seen in autoimmune myasthenia, where muscles of the eyes and oropharynx are almost always affected). End-plate currents are slow to decay, and there is abnormal prolongation of channel opening. The mutations probably act both by increasing the affinity of the nicotinic ACh receptor for ACh, thereby prolonging the effects of this transmitter, and by directly slowing the channel closing rate. In some instances, quinidine is effective therapy for slow channel syndrome because it blocks the open receptor-channel. As with ACh-esterase mutations, end-plate function degenerates due to excessive postsynaptic stimulation, so anticholinesterase medications are potentially dangerous.

In the fast channel syndrome, a different set of mutations in one or more nicotinic ACh receptor subunits leads to an accelerated rate of channel closing and end-plate current decay. The fast channel syndrome may respond to either acetylcholinesterase inhibitors or 3,4-diaminopyridine. The latter blocks a presynaptic potassium conductance and thereby increases the probability of quantal release of ACh, probably by prolonging the action potential.

Lambert-Eaton Syndrome and Botulism Also Alter Neuromuscular Transmission

Some patients with cancer, especially small-cell cancer of the lung, have a syndrome of proximal limb weakness and a neuromuscular disorder with characteristics that are the opposite of those seen in myasthenia gravis. Instead of a decline in synaptic response to repetitive nerve stimulation, the amplitude of the evoked potential increases; that is, neuromuscular transmission is facilitated. Here, the first postsynaptic potential is abnormally small, but subsequent responses increase in amplitude so that the final summated potential is two to four times the amplitude of the first potential.

This disorder, *Lambert-Eaton syndrome*, is attributed to the action of antibodies against voltage-gated Ca^{2+} channels in the presynaptic terminals. It is thought that these antibodies react with the channels, degrading the channels as the antibody–antigen complex is internalized. Calcium channels similar to those of presynaptic terminals are found in cultured cells from the small-cell carcinoma of the lung; development of antibodies against these antigens in the tumor might be followed by pathogenic action against nerve terminals, another kind of molecular mimicry.

A facilitating neuromuscular block is also found in human botulism, as the botulinum toxin also impairs release of ACh from nerve terminals. Both botulism