of a region on chromosome 17 that includes the peripheral myelin protein 22 (*PMP22*) gene. The disease usually presents in the second decade of life as a slowly progressive distal demyelinating motor and sensory neuropathy. CMT1B is caused by mutations in the myelin protein zero gene and accounts for about 9% of genetically defined cases of CMT.

- CMTX encompasses X-linked forms of CMT disease. CMT1X is the most common of these, accounting for 15% of genetically defined cases of CMT. It is linked to mutations in the *GJB1* gene, which encodes connexin32, a gap junction component that is expressed in Schwann cells.
- CMT2 includes autosomal dominant neuropathies associated with axonal rather than demyelinating injury. CMT2A is the most common subtype, accounting for 4% of all CMT disease. It is caused by mutations in the *MFN2* gene, which is required for normal mitochondrial fusion. The phenotype is typically severe, with disease onset in early childhood.

Hereditary sensory neuropathies with or without autonomic neuropathy

This is a diverse group of diseases marked by loss of sensation and variable autonomic disturbances. Loss of pain and temperature sensation is the most common symptom. The inability to sense pain leads to traumatic injury to affected portions of the body. These are typically axonal neuropathies.

Hereditary neuropathy with pressure palsy

This disorder is caused by deletion of the gene encoding *PMP22* (the same gene that is duplicated in CMT1A). It is marked by transient motor and sensory mononeuropathies that are triggered by compression of individual nerves at sites that are prone to entrapment (e.g., the carpal tunnel or the fibular head). Symptoms related to the neuropathy usually resolve within days or weeks, but in some patients the disease eventually progresses to a chronic neuropathy. Swollen, bulbous myelin sheaths at the end of internodes (referred to as *tomaculi*, Latin for a type of sausage) are a characteristic morphologic feature that can be appreciated on special teased fiber preparations of affected nerves.

Familial amyloid polyneuropathies

These are hereditary disorders characterized by amyloid deposition within peripheral nerves. Most are caused by germ line mutations of the transthyretin gene. The mutated transthyretin protein, which is normally involved in serum binding and transport of thyroid hormone, is prone to deposit as amyloid fibrils in a number of tissues, including peripheral nerve (Chapter 6). The clinical presentation is similar to that of hereditary sensory and autonomic neuropathies.

Peripheral neuropathy accompanying inherited metabolic disorders

Several hereditary metabolic disorders are accompanied by peripheral neuropathy during the course of the disease. These include leukodystrophies such as adrenoleukodystrophy (Chapter 28), porphyria (Chapter 25), and Refsum disease, a disorder caused by deficiency of a peroxisomal enzyme.

KEY CONCEPTS

Peripheral Neuropathies

- Anatomic patterns include mononeuropathy, mononeuritis multiplex, polyneuropathy, and polyradiculoneuropathy.
- Damage may occur primarily in Schwann cells (demyelinating neuropathy), axons (axonal neuropathy), or central neurons (neuronopathy); mixed patterns of injury occur.
- Inflammatory disease, infections, metabolic changes, toxic injury, trauma, paraneoplastic disorders, and inherited gene defects can all cause peripheral neuropathy.
- Diabetes mellitus is the most common cause of peripheral neuropathy, which most often presents as a distal symmetric neuropathy.
- Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy are the major acute and chronic acquired demyelinating peripheral neuropathies.
- Inherited peripheral neuropathies are genetically and phenotypically diverse disorders that often present in adulthood and may be marked by sensory, motor, or autonomic dysfunction, alone or in combination.

Diseases of the Neuromuscular Junction

The neuromuscular junction is a complex specialized structure located at the interface of motor nerve axons and skeletal muscle that serves to control muscle contraction. Neuromuscular junctions are found midway along the length of myofibers. Here, the distal ends of peripheral motor nerves branch into small processes that terminate in bulbous synaptic boutons. Upon depolarization, these presynaptic nerve terminals release acetylcholine (ACh) into the synaptic cleft, the space separating the nerve endings from the myofiber membrane (referred to as the *sarcolemma*). The postsynaptic sarcolemma is characterized by complex infoldings and exhibits distinct specializations with localized clustering of acetylcholine receptors (AChR). These receptors are responsible for the initiation of signals leading to muscle contraction.

Regardless of cause, disorders that impair the function of neuromuscular junctions tend to present with painless weakness. Autoantibodies that inhibit key neuromuscular junction proteins are the most common cause of disrupted neuromuscular transmission, as found in myasthenia gravis (literally, *grave weakness*). Understandably, inherited defects in specialized neuromuscular junction proteins are also associated with myasthenic syndromes. Disorders caused by toxins that alter neuromuscular transmission are rarely encountered, but had an important role historically in elucidating how the neuromuscular junction functions.

Antibody-Mediated Diseases of the Neuromuscular Junction

Myasthenia Gravis

Myasthenia gravis is an autoimmune disease that is usually associated with autoantibodies directed against acetylcholine receptors. It has a prevalence of 150 to 200 per million and shows a bimodal age distribution. The