Chapter 19
Disorders of the Nervous System
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Introduction

The nervous system is a complex and intricate system that enables the individual to recognize and react to the environment and to interact with the environment in a meaningful manner. Underlying this complex system is its simplicity of composition, with relatively few distinct cell types including neurons and glial cells. The nervous system is organized into the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS receives, processes, and initiates signals, whereas the PNS relays signals to and from the environment and the CNS. In both systems, the neuron is the principal cell type. Neurons communicate with their targets via long cytoplasmic processes called axons. In the PNS, the peripheral nerves are primarily composed of bundles of axons and their associated Schwann cells. Schwann cells provide protection and trophic support and are found in two phenotypes—myelinating and nonmyelinating. Myelinating Schwann cells ensheath large-caliber axons in myelin and maintain a one-to-one relationship with axons. Myelination increases the speed of action potential propagation and allows signals to reach their targets in a timely manner. In contrast, nonmyelinating Schwann cells associate with numerous axons in structures known as Remak bundles, which enclose small caliber C fibers and transmit pain and temperature sensation. The loss of myelination and changes in Remak bundles are common signs of peripheral nerve neuropathy. This chapter will describe the structure and function of the human nervous system and discuss the pathophysiology of specific neuropathies that are important in orthopaedic clinical practice.

Peripheral nerves are heterogeneous composite structures composed of neurons, Schwann cells, fibroblasts, and macrophages. The neuron is a polarized cell that forms the foundation of the nerve and consists of dendrites, the cell body, and a single axon. The cell body contains the nucleus, cytoplasmic organelles, and a cytoskeleton composed of neurofilaments and microtubules. The axon originates from a unique region of the cell body called the axon hillock, which is the site where the action potential of the neuron is produced. Axons project toward sites of innervation, where they form synapses. Synaptic transmissions from the axon to the end organ are mediated by electrochemical changes.

In the PNS, the axons are surrounded by glial cells called Schwann cells, which produce myelin. If the axonal diameter is greater than or equal to 1 µm, each Schwann cell will wrap its plasma membrane around a single region of an axon and develop myelin. Myelin, composed of 70% lipid and 30% protein, functions to provide fast and efficient conduction of the action potential propagating down an axon. Discontinuities along the length of the axon in the myelin sheath are called the nodes of Ranvier. When the action potential reaches a node, it depolarizes sodium channels. This rapid action potential propagation down the axon from node to node occurs by a process called saltatory conduction. Peripheral nerves have connective tissue layers to provide strength and protection to the nerve with its three layers: the endoneurium, perineurium, and epineurium (Figure 1). The endoneurium surrounds individual axons and their associated Schwann cells. It is composed of thin collagen strands that provide nourishment and protection. Multiple nerve fibers form a collection of axons called a fascicle. Fascicles are grouped and surrounded by the perineurium, which is composed of collagen and fibroblasts. This sheath provides the nerve with tensile strength, and the fibroblasts contribute to the formation of the blood-nerve barrier. Multiple fascicles are grouped together and surrounded by a connective tissue layer called the internal or interfascicular epineurium. This layer cushions the fascicles within the nerve and allows them to move freely against one another. The periphery of the entire nerve is covered by the external or extrafascicular epineurium, which protects the entire nerve from the surrounding environment.

The CNS consists of functions served both in the brain and in the spinal cord. The brain is structurally organized into lobes (the gray matter) named the fron-
The frontal lobes are predominantly tasked with execution of executive and affective functions while the parietal lobes control motor and sensory functions. The temporal lobes focus on memory and cognition while the occipital lobes are concerned with vision. Language is also controlled by these structures. The various lobes connect with each other and the contralateral side through nerve fiber connections (the white matter bundle). There are also specialized nuclei deep within the brain, which are concerned with motor control, sleep, and consciousness and awareness. The caudal portion of the brain is known as the brainstem and is a densely packed region of brain with many vital structures that control autonomic functions, respiration, eye movements, swallowing, and motor and sensory functions.

The spinal cord is a vital portion of the CNS that relays sensory input from the environment to higher levels of the neuraxis, directs motor activity through somatic and visceral motor neurons, possesses intrinsic reflex properties, and influences the activity of spinal neurons through descending tracts. The spinal cord spans the distance from the foramen magnum to the second lumbar vertebrae. Axons enter and exit the spinal cord via the spinal nerves, each of which consists of a ventral or efferent root and a dorsal or afferent root. The ventral roots carry output to the striated muscles from the myelinated nerve fibers of motor neurons in the gray matter of the ventral horn. The dorsal roots carry sensory input from myelinated and unmyelinated nerve fibers that originate from somatic sensory receptors. The cell bodies of the afferent fibers are located in the dorsal root ganglia. The spinal cord is further subdivided into white and gray matter. The descending tracts from the cortex and subcortical parts of the brain and the ascending fiber tracts are organized into well-demarcated and somatotopically arranged columns (Figure 2). These contain both myelinated and unmyelinated nerve axons. The gray matter is contained in the central portion of the spinal cord, which is an X-shaped structure containing longitudinally arranged neuronal cell bodies along with supporting structures such as glial cells, dendrites, and myelinated and unmyelinated axons. The gray matter is divided into the dorsal horn (predominantly sensory), the intermediate zone, and the ventral horn (purely motor). The ventral horn is populated by motor efferent neurons that project their axons out of the CNS via the ventral roots. These axons end up in various muscles in the limb and trunk and represent the pure efferent or motor fibers. The dorsal horns contain the first-order neurons that receive afferent input from the sensory dorsal root ganglion neurons (which in turn receive input from the
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Skin-based and other sensory receptors). The dorsal horn is organized into columns of nerve fibers that travel in a rostral fashion, otherwise known as the “dorsal column.” The dorsal columns are also organized in a lamellar structure, with sensory neurons organized in a topographical fashion. The nerve projection from the dorsal root ganglia enters the dorsal horn of the spinal cord through the dorsal column and synapse with these neurons in the dorsal column. Some of these projections either descend or ascend the dorsal column; some projections bypass the nuclei in the dorsal horns and synapse in the mid portions of the spinal cord and then ascend up in a tract of fibers, known as the spinothalamic tract. Projections within the dorsal columns as well as the spinothalamic tract eventually pass through the brainstem and end in the sensory relay nucleus, the thalamus. Descending nerve fibers from the motor cortex in the brain are organized in the lateral portions of the spinal cord and are known as the lateral corticospinal tract. These fibers, in turn, synapse on the interneurons (see below), which in turn synapse with the motor neurons in the anterior horn cells. This way the descending corticospinal tracts influence motor movements and determine the muscle tone in the extremities as well as deep tendon reflexes. Autonomic tracts and primary autonomic neurons are present in the intermediolateral column of the spinal cord in the thoracic regions; these are the primary autonomic neurons that control a number of autonomic functions, including sphincter control. The intermediate zone contains neurons whose projections remain within the spinal cord and end on another neuron. These interneurons play an important role in generating the spinal reflexes.

Compression Neuropathies

Compression of the neural structures, either intraspinal or extraspinal, leads to neurologic dysfunction. Compression of the spinal cord within the spinal canal, either through an extrinsic lesion, such as bony outgrowth, herniated disks, bleeding (hematoma), lipoma, or metastatic lesions, or through an intrinsic lesion, such as a nerve or meningeal tumor, may create a neurologic emergency with the restoration of neurologic functions dependent on the timing of response to correct such abnormalities. Nerve compression can occur outside the spinal canal, either in the exit zone, as the nerve roots exit the spinal canal, or along the length of the nerve, often at predictable sites of entrapment. Common causes of entrapment are ligamentous or fibrous outgrowths that “pinch” a nerve. Bony outgrowth (osteophytes) in the joints or bones may also impinge a nerve. Rarely tumors (neurofibroma or lymphoma), inflammatory conditions, such as meningeal adhesions, as in arachnoiditis or amyloid deposits, or trauma may cause such entrapments.

Compression neuropathies of the upper extremity frequently occur and may require surgical treatment. Pathologic changes in peripheral nerves result from external mechanical forces of compression, with the
Symptoms described by patients commonly referred to as entrapment syndromes. The defining objective feature of compression neuropathies is the progressive decline in nerve conduction velocity. Chronic nerve compression injuries of the median, ulnar, and radial nerves occur in predictable locations in the wrist, forearm, and arm. Overuse and cumulative trauma in areas of restricted anatomic space can lead to compression of the nerve. The pathophysiologic changes include slowing of nerve conduction velocity, ischemia, edema, and eventually, neuropathy, which includes Schwann cell phenotypic changes, demyelination, and axonal dysfunction.

Nerve changes have classically been defined on the basis of the ensuing morphologic changes. Even with the most severe injuries to a nerve, the segment of nerve distal to the site of injury is able to maintain its integrity up to 3 to 7 days after injury. This is true even after complete injuries, where all connections to the proximal segment of the nerve, and thus the neuronal structures in the spinal cord (either the motor neurons or dorsal root ganglia), are severed. After nerve injury, the distal segment of the nerve starts to disintegrate to prepare for neural regeneration through a series of coordinated events known as wallerian degeneration. This process is initiated by granular disintegration of the axonal cytoskeleton with the ensuing recruitment of hematogenously derived macrophages. With the myelin and axonal debris cleared, the remaining Schwann cells proliferate and the distal segment is known as the bands of Bugner. Neural injuries however, are variable and may be incomplete with damage only to either the myelin sheath, with resulting segmental demyelination, or only the axon, with resulting axonal degeneration without damage to the myelin. The Seddon classification helped prognosticate these injuries. The mildest injury is when only the myelin sheath is damaged without damage to the axon. This form, known as neurapraxia, has the best prognosis. Damage to axons is termed axonotmesis, and usually is reversible, especially if only a short segment of the axon is damaged. The prognosis is fair, and recovery is possible albeit never complete and not as good as in the case of neurapraxia. However, if there is a large segment of axonal damage or if there is severe injury which not only damages the axon but the surrounding neural structures, the most severe form of nerve injury. This form was termed neuromatosis, and implies a “dying back” phenomenon where the proximal segment of the nerve (in addition to the degeneration of the distal segment – wallerian degeneration) disintegrates and the primary neurons resultantly undergo chromatolysis and eventual death.

Recent studies have shown the pathophysiology of neuropathy resulting from compression at the cellular and molecular levels. Chronic nerve compression injuries of peripheral nerves are distinctly different from acute injuries such as those caused by crushing and transection. Initially, it was believed that axonal damage during chronic nerve compression injury triggers Schwann cells dedifferentiation and proliferation. However, research has indicated that axonal integrity is maintained and is free of pathology in chronic nerve compression injuries. Compression neuropathies do not show morphometric evidence of wallerian degeneration, the hallmark of acute peripheral nerve injuries. Furthermore, chronic nerve compression injuries occur in the absence of the early, dramatic inflammation and immune-mediated responses that occurs with acute injuries. Chronic nerve compression injuries also lead to subsequent demyelination and remyelination of injured axons. Thinner myelin is formed on remyelination, with this decrease in myelination contributing to the clinical presentation of slowing nerve conduction velocity in electrodiagnostic studies. Chronic nerve compression injury also has been shown to induce a phenotypic switch in the Schwann cell phenotype. An increase in the number of nonmyelinating Schwann cells and Remak bundles is observed in chronic nerve compression injuries. These Remak bundles contain an increased number of C fibers, which correlate with the pain at compression sites in compressive neuropathies. Schwann cells are mechanically sensitive to shear forces and the expression of specific surface adhesion proteins are altered in response to hydrostatic pressure.

Thus, current research supports the belief that compression neuropathies are primarily a Schwann cell-mediated disease. By further understanding the mechanism of injury response by Schwann cells to mechanical stimulation, molecular therapies can be developed to prevent injury and promote regeneration.

**Electrodiagnostic Studies**

Nerve conduction studies and needle electromyography (EMG) are important tools in localizing areas of compression and neuropathy within the peripheral nervous system. Electrodiagnostic studies are useful in distinguishing a root lesion from compression at the spinal level from trunk, division, or cord compression at the brachial or lumbar plexus, and branch compression peripherally. These studies also help determine the severity of the lesion and can be used to determine the prognosis of the lesion (neurapraxia with good prognosis versus axonotmesis/neurotmesis with a poor prognosis. Nerve conduction studies can further distinguish an axonal pathology from a demyelinating pathology and can distinguish a neurogenic lesion from a myopathic lesion. These studies complement the information obtained through imaging modalities.

Nerve conduction velocity studies are routinely performed on peripheral nerves to determine their responsiveness to electrical stimuli. A constant voltage electrical stimulator is used to evoke a response that is recorded either from a muscle in a motor nerve study or along the nerve in a sensory nerve study. The latency of the response (the time from the onset of the stimulus to the onset of the recorded response) is calculated and displayed in milliseconds. The distance that the stimulus had to travel (from the cathode of the stimulating electrode to the active recording electrode) is then measured with this distance then divided by the latency to obtain the nerve conduction velocity. Because motor...
nerve studies include a transit through the neuromuscular junction, where an inherent delay occurs, an additional stimulus is given along a proximal segment of the nerve, and the conduction velocity is calculated along the nerve, between the two points of stimuli (to compensate for the delay at the neuromuscular junction). The amplitude of the response also is calculated. All of the responses are compared to normative data to determine if they are normal or abnormal. A conduction block is a delay in the conduction velocity with a decrease in the amplitude of the compound action potential from the nerve across a site of injury. A conduction block occurs because of impaired conduction across the injured segment of the nerve, with either a partial or a complete disruption of conduction. This results in a normal distal response (distal to the site of injury) but an abnormal response as the stimulator is moved proximal to the site of the injury.

An axonal injury to the nerve primarily creates a decreased amplitude on electrophysiologic examination. The latency and conduction velocity are not expected to change unless the degree of axonal injury is such that the myelin sheaths are also secondarily affected with the ensuing demyelination. In that situation, a slight prolongation in latency and slowing in conduction velocity would also occur. Demyelinating lesions primarily affect the latency of the response and thus the conduction velocity. Amplitudes would only be affected with demyelinating lesions if there is a severe block in conduction or severe desynchrony of conduction created by segmental demyelination which results in a temporal dispersion of the response. Myopathic lesions tend to affect the amplitude of the motor nerve response because the motor responses are recorded from muscles; sensory nerve studies are not affected by myopathies. Table 1 details the changes seen with nerve conduction velocity studies in various nerve and muscle lesions.

Additional electrophysiologic studies can be performed to determine late responses in the motor nerve. These responses are known as F-waves (because the waves were initially recorded in the foot muscles) and are particularly useful for evaluating conduction problems in the proximal region of nerves such as in portions of nerves near the spinal cord. These studies are also very useful in evaluating disorders that affect the proximal region of nerves such as radiculopathy or with a demyelinating disease such as Guillain-Barré syndrome. Another electrophysiologic study that is equally useful is the Hoffman reflex or H-reflex. The H-reflex is a true reflex with both an afferent and an efferent limb to the reflex. It is obtained by electrical stimulation of I-α afferent fibers at the knee with recording from the soleus. The resulting electrical stimulation is carried back to the spinal cord by the I-α afferents to the S1 level and then transmitted by synapses on to the anterior horn cells at that level. This results in a motor nerve discharge that can be recorded from the soleus muscle. The H-reflex is affected by sensory neuropathies, motor disorders affecting the sciatic or tibial nerves, and is asymmetrically affected by S1 root lesions.

Needle EMG studies provide complementary information to nerve conduction velocity studies regarding the state of health of the skeletal muscles. These muscles can be affected by primary disease of the nerve roots, the peripheral nerves, or the skeletal muscles themselves. EMG studies help differentiate and discriminate between the various conditions. EMG studies also can determine if the nerve lesions are acute or chronic and if reinnervation has occurred. In patients with a nerve injury, this information, along with nerve conduction velocity studies, helps determine whether the nerve continuity is maintained.

To perform intramuscular EMG, a needle electrode is inserted through the skin into the muscle tissue. A trained physician such as a neurologist or a physiatrist observes the electrical activity while inserting the electrode. The insertional activity provides valuable information about the state of the muscle and its innervating nerve. Normal muscles at rest produce certain normal electrical sounds when the needle is inserted into them. This baseline electrical activity is evaluated when the muscle is at rest. Abnormal spontaneous activity often indicates some nerve and/or muscle damage. Subsequently, the patient is asked to contract the muscle smoothly. The shape, size, and frequency of the resulting motor unit potentials are judged. The electrode is then retracted a few millimeters, and the activity is analyzed again until at least 10 to 20 units have been collected. Each electrode track gives only a very local picture of the activity of the whole muscle. Because the inner structures of the skeletal muscles differ, the electrode must be placed at various locations to obtain an accurate study. Table 2 describes the changes seen on EMG studies in various pathologic conditions.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Latency</th>
<th>Conduction Velocity</th>
<th>Amplitudes</th>
<th>F-Wave Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve-axonal</td>
<td>Normal</td>
<td>Normal</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
<tr>
<td>Nerve-demyelinating</td>
<td>Prolonged</td>
<td>Slow</td>
<td>Normal or reduced</td>
<td>Absent or prolonged</td>
</tr>
<tr>
<td>Myopathy</td>
<td>Normal</td>
<td>Normal</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td>Normal</td>
<td>Normal</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
</tbody>
</table>


**Table 2**

Findings on Needle Electromyography Studies in Various Neuromuscular Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Insertional Activity</th>
<th>Spontaneous Activity</th>
<th>Motor Unit Morphology</th>
<th>Recruitment</th>
<th>Firing Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurogenic: &lt; 7 days</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Neurogenic: 7 days to 3 months</td>
<td>Increased</td>
<td>Fibrillations and fasciculations; complex repetitive discharges</td>
<td>Increased amplitude and duration; variable polyphasia</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Neurogenic: &gt; 3 months</td>
<td>Increased</td>
<td>Fibrillations and fasciculations; complex repetitive discharges</td>
<td>Decreased amplitude and duration; variable polyphasia</td>
<td>Early</td>
<td>Normal</td>
</tr>
<tr>
<td>Myopathy: with inflammatory or necrotic elements</td>
<td>Increased</td>
<td>Fibrillations; myotonia; complex repetitive discharges</td>
<td>Decreased amplitude and duration; variable polyphasia</td>
<td>Early</td>
<td>Normal</td>
</tr>
<tr>
<td>Myopathy: with no inflammatory or necrotic elements</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal; decreased amplitude and duration</td>
<td>Normal or early</td>
<td>Normal</td>
</tr>
<tr>
<td>Neuromuscular junction disorder</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Electrophysiologic Response to Acute Nerve Injury**

Because myelin can be repaired, unless there is secondary involvement of the axonal structures, neurapraxia has a good prognosis with complete recovery over several weeks. Surgery for repair of the nerve is often not needed and patients should be carefully followed with serial electrodagnostic studies. A more severe injury may produce axonotmesis. In addition to the disruption of myelin, the axonal tube is also damaged; however, the surrounding neural structures (the neural tube) are intact. Thus, the architectural framework for the nerve remains intact and the recovery potential is fair. With severe or large lesions, recovery may not be as robust. Surgery to perform neurolysis or bridge the defect may be required to allow maximal neural regeneration. Because axonal structures are damaged in situations with severe or large lesions, the amplitude of evoked responses on nerve conduction velocity studies decreases progressively and often may be absent. As the injury may affect both sensory and motor nerves, needle EMG examination shows evidence of denervation, such as fibrillation potentials and the reduced recruitment of motor units. In acute stages, motor units may be absent in patients with severe injuries. Follow-up studies are even more crucial in this situation, especially in patients with severe injuries, because nerve conduction changes may reverse (improve) and needle EMG examination may begin showing signs of reinnervation.

In neurotmesis, the most severe form of neural injury, all the neural structures are damaged, which results in complete disruption of the neural architecture. Nerves have inherent elastic properties, causing retraction of the cut ends and preventing any chance of spontaneous regeneration. Because of the severity of injury, and the lack of trophic support from the neural body, rapid deterioration of nerve axons occurs. Additionally, a dying-back of axons extends all the way back to the cell body (neurons) resulting in cell death. The prognosis is poor and very early surgical intervention is required in some instances to improve recovery potential. Electrophysiology shows complete absence of nerve conduction in the affected nerves. Three days after injury, EMG will show profuse denervation.

**Neuropathies Associated With Systemic Illnesses**

A number of systemic conditions have pathologic involvement of peripheral nerves, including diabetes mellitus, uremia, thyroid disorders and nutritional deficiencies. The degree of involvement is variable as not every patient with such systemic illnesses has nerve involvement. In patients with systemic disorders, diabetes mellitus, hypothyroidism, and vitamin B₁₂ deficiency routinely appear to be the most common conditions associated with neuropathies.

**Diabetes**

Diabetic neuropathy is a relatively common condition that is associated with multiple phenotypes and is estimated to be the cause of neuropathy in 15% to 30% of North American patients. Diabetes mellitus is associated with several types of polyneuropathies: distal symmetric sensory or sensorimotor polyneuropathy, autonomic neuropathy, diabetic neuropathic cachexia, polyradiculoneuropathies, cranial neuropathies, and other mononeuropathies (Table 3). The exact prevalence of each subtype of neuropathy in diabetic patients is not accurately known; however, it has been estimated...
that neuropathy will develop in 5% to 66% of patients with diabetes.\textsuperscript{1,2} Alarmingly, diabetic neuropathy can also occur in children. Long-standing, poorly controlled diabetes mellitus and the presence of retinopathy and nephropathy are risk factors for the development of peripheral neuropathy in diabetic patients. In a large community-based study, 1.3% of the population had diabetes mellitus (type 1, 27%; type 2, 73%). Of these, approximately 66% of individuals with type 1 diabetes mellitus had some form of neuropathy: generalized polyneuropathy, 54%; asymptomatic carpal tunnel syndrome, 22%; symptomatic carpal tunnel syndrome, 11%; autonomic neuropathy, 7%; and various other mononeuropathies and/or multiple mononeuropathies, 3%, which included ulnar neuropathy, peroneal neuropathy, lateral femoral cutaneous neuropathy, and diabetic amyotrophy.\textsuperscript{13} In the group with type 2 diabetes mellitus, 45% had generalized polyneuropathy, 29% had asymptomatic carpal tunnel syndrome, 6% had symptomatic carpal tunnel syndrome, 5% had autonomic neuropathy, and 3% had other mononeuropathies and/or multiple mononeuropathies. Considering all forms of diabetes mellitus, 66% of patients had some type of objective sign of a diabetic neuropathy, but only 20% of patients with diabetes mellitus were symptomatic.

Distal symmetric sensory polyneuropathy is the most common form of diabetic neuropathy. It is a length-dependent neuropathy in which sensory loss begins in the toes and gradually progresses over time up the legs and into the fingers and arms. When severe, sensory loss may also develop in the midline of the trunk (chest and abdomen) and spread laterally toward the spine. The sensory loss is often accompanied by paresthesias, lancinating pains, burning sensations, and/or a deep aching discomfort. A severe loss of sensation can lead to increased risk from trauma to the extremities, with secondary infection, ulceration, and Charcot joints. Signs of an autonomic dysfunction may develop in patients with small fiber neuropathy because the autonomic nervous system is mediated by small myelinated and unmyelinated nerve fibers. Poor control of diabetes mellitus and the presence of nephropathy correlate with an increased risk of developing distal symmetric sensory polyneuropathy.

A neurologic examination will show loss of small fiber function, that is, pain and temperature sensation, and may also show a panmodality sensory loss. Those with large-fiber sensory loss have reduced muscle stretch reflexes, particularly at the ankles; however, reflexes can be normal in patients with only small-fiber involvement. Muscle strength and function are typically normal, although mild atrophy and weakness of intrinsic foot muscles and ankle dorsiflexors may be detected. Because patients without motor symptoms or signs on clinical examination will often have electrophysiologic evidence of subclinical motor involvement, the term distal symmetric sensorimotor peripheral neuropathy is also appropriate.

The diagnosis of diabetic neuropathy is dependent on the fulfillment of criteria outlined by the American Diabetes Association in conjunction with one or more of the characteristic clinical diabetic neuropathy phenotypes.\textsuperscript{14} The American Diabetes Association criteria include either an elevated fasting blood glucose level (≥124 mg/dL) or an abnormal 2-hour glucose tolerance test (≥200 mg/dL). Tests of glycosylated hemoglobin are usually used to assess diabetic control rather than for the initial detection of diabetes. Traditionally, neuropathy was not readily attributed to diabetes unless the diagnosis of diabetes had been established for years. More recently, a statistical association was demonstrated between impaired glucose tolerance (fasting blood sugars between 110 to 125 mg/dL; or a 2-hour serum glucose, after a 75-g glucose challenge following a 12-hour fast, 140 to 199 mg/dL) and a small-fiber neuropathy phenotype (see below).

Up to 50% of asymptomatic patients with diabetes mellitus have reduced sensory nerve action potential amplitudes along with slowed conduction velocities of the sural or plantar nerves, whereas up to 80% of symptomatic patients have abnormal sensory nerve conduction velocity studies. Quantitative sensory testing may show reduced vibratory and thermal perception. Autonomic testing may also be abnormal, particularly, quantitative sweat testing. Biopsies of nerves of patients with diabetes can show axonal degeneration, clusters of small regenerated axons, and segmental demyelination that is more pronounced distally, as expected in a length-dependent process. Although not clearly defined, the major theories about the pathogenesis of diabetic neuropathy involve a metabolic process, microangiopathic ischemia, or an immunologic disorder.\textsuperscript{15}

The mainstay of treatment is strict control of glucose, which can reduce the risk of developing a neuropathy or can improve an existing neuropathy.\textsuperscript{16,17} Pancreatic transplantation may stabilize or slightly improve sensory, motor, and autonomic function.\textsuperscript{18} More than 20 trials of aldose reductase inhibitors have been performed and most have had negative results. Trials of neurotrophic growth factors also have been disappointing. A double-blind study of α-lipoic acid, an antioxidant, reported significant improvement in neuropathic sensory symptoms such as pain and several other neuropathic end points.\textsuperscript{19}

### Table 3

<table>
<thead>
<tr>
<th>Various Neuropathic Syndromes Associated With Diabetes Mellitus and Hypoglycemia</th>
</tr>
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<tbody>
<tr>
<td><strong>Diabetes Mellitus</strong></td>
</tr>
<tr>
<td>Distal symmetric sensory and sensorimotor polyneuropathy</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
</tr>
<tr>
<td>Diabetic neuropathic cachexia</td>
</tr>
<tr>
<td>Radiculoplexus neuropathy</td>
</tr>
<tr>
<td>Mononeuropathy/multiple mononeuropathies</td>
</tr>
<tr>
<td><strong>Hypoglycemia and Hyperinsulinemia</strong></td>
</tr>
<tr>
<td>Generalized sensory or sensorimotor polyneuropathy</td>
</tr>
</tbody>
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Orthopaedic Knowledge Update 10
Hypothyroidism
Although hypothyroidism is more commonly associated with a proximal myopathy, neuropathy develops in some patients, most typically carpal tunnel syndrome. Although rare, some patients may develop a generalized sensory polyneuropathy characterized by painful paresthesias and numbness in the hands and the legs. Pharmacologic correction of hypothyroidism usually halts disease progression and may improve polyneuropathy.

Inflammatory Neuropathies

Some patients develop an autoimmune response toward peripheral nerves with the immune attack directed against peripheral nerve antigens such as myelin protein zero or myelin-associated glycoprotein. In certain disorders, autoimmunity develops as an aberrant response to the normal immune response to bacterial infections. A good example of this is the autoimmunity to nerve gangliosides in patients with Campylobacter jejuni diarrheal infections. Two immune neuropathies – chronic inflammatory demyelinating polyradiculopathy (CIDP) and multifocal motor neuropathy (MMN) will be discussed.

CIDP is a dynamic immune-mediated neuropathy characterized by either a progressive or relapsing course. The diagnostic approach requires a detailed clinical examination, the findings of electrodiagnostic abnormalities, and occasionally, a nerve biopsy. CIDP may account for 10% to 33% of initially undiagnosed peripheral neuropathies in large tertiary referral centers. By definition, the symptoms and signs of the neuropathy must be progressive for at least 2 months, which distinguishes CIDP from Guillain-Barré syndrome or the most common form of this disorder, acute acquired inflammatory demyelinating neuropathy. Differentiating an acute acquired inflammatory demyelinating neuropathy from CIDP can be difficult in the first few weeks of disease onset because it is not always possible to determine if the disease will continue to progress for at least 2 months or will reach a plateau. Four courses of progression in patients with CIDP have been described: (1) chronic monophasic, in 15% of patients; (2) chronic relapsing with fluctuations of weakness or improvement over weeks or months, in 34%; (3) stepwise progressive, in 34%; and (4) steady progressive, in 15%. In this respect, CIDP is similar to multiple sclerosis, an immune-mediated demyelinating disorder affecting the CNS.

CIDP usually presents in adults (peak incidence at approximately 40 to 60 years of age) with a slightly increased prevalence in men. Most patients manifest with progressive, symmetric proximal, and distal weakness of the arms and legs. Early in the course of the illness, only distal extremity numbness and weakness may be apparent. If the weakness remains distal, other diagnoses should be considered. Although most patients (at least 80%) have both motor and sensory involvement, a few patients may have pure motor (10%) or pure sensory (5% to 10%) symptoms and signs. Subjective numbness in the extremities is present in 68% to 80% of patients, whereas painful paresthesia occurs in 15% to 50%. The sensory examination is abnormal in most patients, particularly in large-fiber modalities (vibration and touch). Most patients with CIDP are areflexic or at least hyporeflexic. Most patients (80% to 95%) have an elevated cerebrospinal fluid protein level (> 45 mg/dL) with a mean of 135 mg/dL; some levels may be greater than 1,200 mg/dL. Similar to Guillain-Barré syndrome, the cerebrospinal fluid cell count is usually normal. Elevated cerebrospinal fluid cell counts should lead to the consideration of HIV infection, sarcoidosis, Lyme disease, or lymphomatous or leukemic infiltration of nerve roots. Motor conduction studies evaluating compound muscle action potential amplitudes, distal latencies, conduction velocities, and F-wave latencies, as well as studies that look for evidence of temporal dispersion or a conduction block, are the most useful electrodiagnostic tools for CIDP. Most patients with CIDP have low-amplitude or unobtainable sensory nerve action potentials in both the upper and the lower extremities. Nerve biopsies are helpful in making the diagnosis because evidence of segmental demyelination and remyelination is often present. Although not specific for CIDP, this chronic demyelination and remyelination results in proliferation of surrounding Schwann cell processes, forming the so-called onion bulbs. Nerve biopsies are particularly useful when lymphomatous infiltration, amyloidosis, and sarcoidosis are considered in the differential diagnoses because these disorders can mimic CIDP.

Although CIDP is an autoimmune disorder, the antigen(s) to which the immune attack is targeted and the specific roles of the humoral and cellular system in the pathogenesis of CIDP are not known. Corticosteroids, plasmapheresis, and infusion of intravenous immunoglobulins have been shown to be beneficial in treating patients with CIDP. Intravenous immunoglobulins have become the treatment of choice because it has fewer long-term adverse side effects than corticosteroids. Of importance, patients treated early are more likely to respond, underscoring the need for early diagnosis and treatment.

In contrast, multifocal motor neuropathy (MMN) is an immune-mediated demyelinating neuropathy characterized clinically by asymmetric weakness and atrophy, typically in the distribution of individual peripheral nerves. MMN is often misdiagnosed as amyotrophic lateral sclerosis (ALS). Weakness in patients with MMN occurs in the distribution of individual peripheral nerves, whereas in ALS the weakness is in distribution of myotomes. MMN has a much lower incidence than ALS. MMN has a male predominance (male-to-female ratio of approximately 3:1) and an age of symptom onset usually ranging from the second to the eighth decades of life, with most occurring in the fifth decade of life. Onset in childhood is rare. Focal muscle weakness accompanied by cramps and fasciculations is usually first noted in the distal arms; however,
weakness can initially develop in the legs. Most patients present with intrinsic hand weakness, wrist drop, or foot drop. The onset is usually insidious, and the weakness typically progresses over the course of several years to involve other limbs. As with CIDP, treatment of MMN can be complicated with relapses, and often patients become unresponsive to previously effective treatment.

As the name implies, MMN involves two or more motor nerves. However, MMN usually starts as a mononeuropathy. Cases of monofocal motor neuropathy may represent the early presentation of MMN and should be treated as such. The electrophysiologic hallmark of MMN is a persistent conduction block in motor nerves in segments not usually associated with compression or entrapment. Sensory nerve biopsies in MMN are usually normal, although a slight reduction in myelinated fibers or axonal degeneration has been seen. Because sensory nerves are spared, the autoimmune attack is likely directed against an antigen that is relatively specific for the motor nerve. Although ganglioside antibodies are common, the pathogenic role for these antibodies is not known.

Unlike in patients with CIDP, patients with MMN generally do not respond to corticosteroids or plasmapheresis. MMN is typically responsive to intravenous immunoglobulins. Rituximab also has recently been used to treat immune-mediated neuropathies, including MMN. Rituximab is a monoclonal antibody that binds to the CD20 antigen on normal and malignant B lymphocytes, destroying these cells. It is approved to treat B cell lymphoma and reduces peripheral B lymphocyte counts by 90% within 3 days.

### Neuropathies Associated With Infections

Nerves are commonly involved in human infectious disorders. In certain conditions, nerve involvement may occur secondary to direct invasion. For instance, both the herpes simplex virus and the HIV virus are neurotropic and preferentially attack peripheral nerves. In other infectious conditions, nerve involvement may occur secondary to infection of the surrounding tissues or due to complications of treatment such as with leprosy.

### Leprosy

Leprosy is caused by infection with the acid-fast bacteria *Mycobacterium leprae*. Leprosy is the most common cause of peripheral neuropathy in Southeast Asia, Africa, and South America. This infection has a spectrum of clinical manifestations ranging from tuberculoid leprosy to borderline leprosy to lepromatous leprosy. The clinical manifestations of the disease are determined by the immunologic response of the host to the infection. In tuberculoid leprosy, the cell-mediated immune response is intact, with focal, circumscribed inflammatory responses to the bacteria within the affected areas of the skin and nerves. The resulting skin lesions appear as well-defined, scattered, hypopigmented patches and plaques with raised, erythematous borders. Cutaneous nerves are often involved, resulting in a loss of sensation in the center of the skin lesions. Cooler regions of the body such as the face and limbs are more susceptible than warmer regions such as the groin or axilla. The most common sites of involvement are the ulnar nerve at the medial epicondyle, the median nerve at the distal forearm, the peroneal nerve at the fibular head, the sural nerve, the greater auricular nerve, and the superficial radial nerve at the wrist. The nerves become thickened and encased with granulomas, leading to mononeuropathy or mononeuropathy multiplex.

In lepromatous leprosy, cell-mediated immunity is severely impaired, leading to extensive infiltration of the bacilli and hematogenous dissemination, which produces confluent and symmetric areas of rash, anesthesia, and anhidrosis. The clinical manifestations tend to be more severe in the lepromatous subtype. As in the tuberculoid form, there is a predilection for involvement of cooler regions of the body. Infiltration of the organism in the face leads to the loss of eyebrows and eyelashes and exaggeration of the natural skin folds, leading to the so-called leonine facies. Superficial cutaneous nerves of the ears and distal limbs are also commonly affected. A slowly progressive symmetric sensorimotor polyneuropathy gradually develops because of widespread invasion of the bacilli into the epineurium, perineurium, and endoneurium. Distal extremity weakness may be seen, but large sensory fiber modalities and muscle stretch reflexes are relatively spared. Involvement of nerve trunks leads to superimposed mononeuropathies, including facial neuropathy.

Leprosy is usually diagnosed with a skin lesion biopsy and the Fite acid-fast staining method. Nerve biopsies also can be diagnostic, particularly when there are no apparent skin lesions. The immune response of the host to the bacilli determines the histopathology. The tuberculoid form is characterized by granulomas formed by macrophages and T helper 1 lymphocytes—caseation may be present, with typical lesions extending throughout the dermis. Importantly, bacilli are not seen. In contrast, in lepromatous leprosy, a large number of infiltrating bacilli, T helper 2 lymphocytes, and organism-laden foamy macrophages with minimal granulomatous infiltration are evident. Borderline leprosy can have histologic features of both tuberculoid and lepromatous leprosy. Polymerase chain reaction also may be used in making the diagnosis.

Patients are generally treated for 2 years with multiple pharmacologic agents, including dapsone, rifampin, and clofazimine. Other medications include thalidomide, perfloxacin, ofloxacin, sparfloxacin, minocycline, and clarithromycin. Treatment is sometimes complicated by the so-called reversal reaction, particularly in patients with borderline leprosy. This reversal reaction can occur at any time during treatment and develops because of a shift in the disease phenotype to the tuberculoid end of the spectrum with an increase in cellular immunity during treatment. The cellular response is upregulated, as evidenced by an increased release of
tumor necrosis factor-α, gamma-interferon, and interleukin-2 with new granuloma formation. This can result in an exacerbation of the rash and the neuropathy as well as the appearance of new lesions. High-dose corticosteroids blunt this adverse reaction and may even be used prophylactically in high-risk patients at the onset of treatment. Preventing leprosy is of primary importance. It is recommended that children exposed to leprosy in the household be prophylactically treated with rifampin daily for 6 months.

Lyme Disease
Lyme disease is caused by infection with *Borrelia burgdorferi*, a spirochete, transmitted by ticks. The deer tick, *Ixodes dammini*, is usually responsible for the disease. The ticks acquire the spirochetes by feeding on an infected host (such as deer) and then transmit the spirochetes to the next hosts (such as humans) at a later feed. It takes approximately 12 to 24 hours of tick attachment to transfer the spirochetes to the next host. There are three recognized stages of Lyme disease: (1) early infection with localized erythema migrans, (2) disseminated infection, and (3) late-stage infection.

Neurologic complications may develop during the second and third stages of infection. Facial neuropathy is most common and is bilateral in approximately 50% of patients, which is rare in the differential diagnosis of Bell palsy. Involvement of nerves is frequently asymmetric. The presentation with a polyradiculoneuropathy may resemble Guillain-Barré syndrome.30 Approximately 50% of patients have numbness, paresthesia, weakness, and cramps in the distal extremities; proprioception and vibration are reduced along with muscle stretch reflexes.

Immunofluorescent or enzyme-linked immunoabsorbent assay may detect antibodies directed against the spirochete. Because false-positive reactions are common, Western blot analysis should be performed to confirm a positive enzyme-linked immunoabsorbent assay. Examination of the cerebrospinal fluid should show lymphocytic pleocytosis and increased protein in patients with polyradiculitis, cranial neuropathies, and CNS involvement.31

The recommended treatment of facial nerve palsies in adults is the combination of amoxicillin plus probenecid for 2 to 4 weeks. Patients who are allergic to penicillin can be treated with doxycycline for 2 to 4 weeks. Adult patients with other types of peripheral neuropathy are treated with intravenous penicillin or ceftriaxone for 2 to 4 weeks. Those allergic to penicillin should be treated with doxycycline for 30 days.

Charcot-Marie-Tooth Disease
Charcot-Marie-Tooth disease, ALS, and Friedreich ataxia. See chapter 63 for additional information on neuromuscular disorders. Although a detailed description of muscular dystrophies is beyond the scope of this chapter, the most common form is Duchenne muscular dystrophy, which is an X-linked muscular dystrophy, and is invariably fatal. The disease occurs secondary to a mutation in the dystrophin gene and is characterized by progressive proximal muscle weakness. Achilles tendon contractures are common early in the disease with a progressive loss of ambulation occurring by 10 years of age. Once the children are wheelchair-bound, scoliosis ensues and contributes to progressive respiratory insufficiency. If conservative management including physical therapy and orthosis fail to correct the contracture, surgical correction may be required to prevent loss of ambulation. Surgical correction of thoracic spine scoliosis is also recommended if the degree of scoliosis exceeds 40° and if there is evidence for progressive respiratory insufficiency.

Another neuromuscular disorder with prominent scoliosis is Friedreich ataxia, an autosomal recessive disorder of the spinal cord, which predominantly affects the dorsal columns, resulting in progressive sensory ataxia. Scoliosis occurs early and often is disproportionate to the amount of neurologic dysfunction. As in Duchenne muscular dystrophy, scoliosis results in progressive respiratory dysfunction, and thus eventually needs surgical correction.

Charcot-Marie-Tooth Disease
Hereditary neuropathies may account for as many as 50% of previously undiagnosed peripheral neuropathies referred for treatment to large neuromuscular centers. CMT disease is the most common type of hereditary neuropathy with the pathology focused on the Schwann cell. Rather than just one disease, CMT is a syndrome of several genetically distinct disorders.32 The various subtypes of CMT are classified according to the nerve conduction velocities and presumed pathology (demyelinating or axonal), mode of inheritance (autosomal dominant or X-linked), age of onset (infancy, childhood, or adulthood), and the specific mutated genes. Type 1 CMT is the most common form, with individuals usually presenting with distal leg weakness in the first to third decades of life. There is an early predilection for the anterior compartment (peroneal muscle group), which results in progressive foot drop. This leads to poor clearance of the toes when walking, particularly on uneven surfaces. Patients with type 1 CMT often report frequent tripping, falling, and recurrent ankle sprains. Affected patients generally do not report numbness or tingling, which can be helpful in distinguishing CMT from acquired forms of neuropathy.

Although patients with type 1 CMT usually do not report sensory loss, reduced sensation in all modalities is apparent on examination. Muscle stretch reflexes are unobtainable or reduced throughout the body. There is often atrophy of the muscles below the knee (particularly in the anterior compartment), leading to the so-called inverted champagne bottle legs. However, in rare instances, patients have asymmetric pseudohypertrophy.
of the calves. Most will have pes cavus, equinovarus, or hammer toe deformities (Figure 3), which lead to ach- ing in the feet. Rather than having a heel strike during ambulation, affected people land flatfooted or on their toes, and thus use a steppage gait to help prevent the toes from catching on the ground. Approximately two thirds of patients with type 1 CMT also have distal weakness and atrophy of the arms. The most severely affected patients may have clawhand deformities.

Even if there is no family history of CMT, family members of patients with possible CMT should be ex- amined to determine if other members have features of the neuropathy. This information can be important in clarifying a diagnosis and in referral for appropriate genetic counseling. In addition to genetic testing, nerve conduction studies are the most important laboratory tests for evaluating patients with suspected CMT dis- ease. The nerve conduction studies are invaluable in de- termining if the patient has an axonal or demyelinating neuropathy and in determining if a demyelinating neu- ropathy is uniform or multifocal, which is useful in disting- uishing CMT from chronic inflammatory demyeli- nating polyneuropathy.35 Although nerve biopsies on patients with suspected type 1 CMT are not routinely performed, a nerve biopsy will be strikingly abnormal. The enlarged gross appearance of the peripheral nerves led to the early designation of type 1 CMT as a hyper- trophic neuropathy.

Type 1 CMT is a genetically heterogeneic disorder. Approximately 85% of patients with CMT type 1A have a 1.5-megabase duplication within chromosome 17p11.2-12 in the gene for peripheral myelin protein 22.34 These patients carry three copies of the PMP22 gene rather than two. In contrast, inheritance of the chromosome with the deleted segment results in af- fected individuals having only one copy of the PMP-22 gene and leads to hereditary neuropathy with liability to pressure palsies.35 Although these mutations are in- herited in an autosomal dominant fashion, de novo mutations can occur. CMT type 1A is likely related to a toxic gain of function. The exact function of peripheral myelin protein 22 in the peripheral nerves is not known, but it may be important in maintaining the structural integrity of myelin, acting as an adhesion molecule, or regulating the cell cycle.

There is currently no cure for CMT disease. Orh- otics play an important role in the rehabilitation of pa- tients; however, proper attention is required to monitor patients for pressure sores. Tendon transfer and muscle transfers are often done to improve function, but there are no systemic studies showing their efficacy. Ankle fusion surgery to treat severe foot drop is not currently favored. A trial of supplementation with ascorbic acid is currently under way to determine if this vitamin will improve neural function in patients with CMT.

**Amyotrophic Lateral Sclerosis**

Motor neuron diseases are categorized by its pathologic affinity for the voluntary motor system including pri- marily the anterior horn cells of the spinal cord, certain motor cranial nerve nuclei, and corticospinal/bulbar tracts. ALS, also known as Lou Gehrig’s disease, is the most notorious of these disorders.36 As in other neuro- degenerative conditions, the clinical course of ALS is one of inexorable progression.37 The cause is unknown except in the small proportion of patients who have fa- milial forms of the disease.

The initial clinical features of ALS may be quite di- verse. Typically, patients seek medical care reporting painless muscle weakness and atrophy.7 These signs are frequently asymmetric and sometimes monomelic at the onset. The initial deficits may be restricted in distribu- tion but involve more than a single nerve or nerve root. In instances in which patients do not seek early medical attention or if physicians do not recognize the signifi- cance of the symptoms, patients may not be seen until their disorder is fairly advanced (Figure 4). Less com- monly, the initial symptoms may include impaired speech or swallowing, reduced head control, or disor- dered breathing.38 Fasciculations are usually first recog- nized by the examining physician rather than by the pa- tient, but may occasionally be the initial manifestation of the disease, particularly in those who have a preex- isting awareness of their significance.37 Fasciculations, in the presence of weakness, particularly if multifocal and continuous, strongly support the diagnosis of a motor neuron disorder.

Fasciculations in the absence of muscle weakness and EMG abnormalities, particularly if restricted in their distribution, are typically benign. Conversely, the absence of fasciculations in patients with painless weakness does not preclude the diagnosis of ALS, par-
particularly in patients with considerable subcutaneous tissue. An increased frequency of muscle cramping is common, which is often elicited during manual muscle testing.

The clinical diagnosis of ALS is dependent on the demonstration of lower motor neuron (LMN) and upper motor neuron (UMN) signs, which progress both within and between different body regions. The most common ALS presentation is a patient with a combination of UMN and LMN features, limited initially in distribution, with the LMN findings typically dominating. The initial involvement is typically distally located in a hand or a foot. Initial weakness may occur in proximal muscles as well. A definite diagnosis cannot be made until these combined UMN and LMN signs spread over a period of months, both within and outside the initially affected body part. A definite diagnosis of ALS is uncommon at the time of the initial examination. However, a combination of UMN and LMN signs in the same segment or a single extremity, in the absence of pain or sensory symptoms, is highly indicative of ALS. Despite the absence of a viable differential diagnosis, many patients have unnecessary surgical procedures for presumed cervical myelopathy or radiculopathy. Patients are referred for further evaluation by a neurologist only after clear progression and worsening of their symptoms. Similarly, weakness of the neck extensors and the resultant neck ptosis (neck drop) is quite common and is often mistakenly believed to be related to cervical stenosis.

With the exception of DNA mutational analysis in a patient with a mutation of the \textit{SOD1} gene, there are no laboratory tests that currently confirm the diagnosis of sporadic ALS or most of the familial ALS genotypes. There are laboratory tests, such as those that measure ventilatory function, forced vital capacity, and maximal expiratory and inspiratory pressure, that are used to monitor the course of the disease and to aid in management decisions. Although these tests may aid in the initial diagnosis, their primary purpose is to monitor progress, predict a prognosis, and aid in medical decision making. There are two primary pathologic features of ALS: (1) degeneration with the loss of myelinated fibers occurs in the corticospinal and corticobulbar pathways and (2) a loss of motor neurons within the anterior horns of the spinal cord and many motor cranial nerve nuclei.

Currently, there are no effective treatments that can reverse or arrest disease progression in patients with ALS. As a result, the major goals in managing motor neuron diseases are to slow disease progression to the extent possible and maintain independent patient function, safety, and comfort. The care of patients with ALS and their families involves education, counseling, and symptom management. Two interventions that are often met with resistance by patients are percutaneous gastrostomy and noninvasive positive pressure support. In view of this, it may be prudent to introduce these concepts before the point in the patient’s illness when these interventions are really needed. Both should be introduced with the idea that they will improve the quality of life rather than the duration of life, even though the latter may be achieved to a certain extent as well. Optimal management of patients with ALS and their families requires extensive effort and resources that undoubtedly surpass the capabilities of any single health care worker.

\textbf{Summary}

It is important to have a working knowledge of neurologic conditions that are routinely encountered in orthopaedic practice. Misdiagnosis may delay treatment.
and result in unnecessary testing and suffering. With the assistance and early input from neurologists, treatment may begin early. Furthermore, orthopaedic interventions such as contracture and scoliosis correction may be required to improve the quality of life for these challenging patients.

### Annotated References


   Unlike acute injuries, the neuromuscular junction is preserved with chronic nerve compression injuries even later after disease progression.


   Macrophage recruitment occurs with all peripheral nerve injuries. As macrophages produce Schwann cell mitogens, they are responsible in part for the increase in number of Schwann cells after acute nerve injuries. This is not true for chronic nerve injuries where hematogenously derived macrophages are responsible for the altered blood-nerve barrier but not the ensuing Schwann cell proliferation.


   Schwann cells are mechanosensitive and have the ability to respond to mechanical stimuli such as hydrostatic compression.


   Chronic nerve compression injury preferentially affects small to medium size neurons. This preferential neuronal response to injury may explain why there is not a decrease in nerve conduction velocity early in the disease process.


   Chronic nerve injury induces a demyelination and remyelination process. C-jun and Krox-20 are critical transcriptional factors in these processes. This study was one of the first to demonstrate an integrin response to compression injuries.


   This book discusses the evaluation and management of neuromuscular disease.


   This review article provides a more comprehensive discussion of electrophysiology for the orthopaedic surgeon.


   The authors discuss common neuromuscular conditions, the pathophysiology of nerve injury, and factors influencing nerve regeneration.


This article provides a guide for the clinician as to how to discriminate between different motor neuron disorders.


Evidence on the management of patients with ALS was systematically reviewed. Topics studied included slowing disease progression, nutrition, and respiratory management. Several recommendations were made.