Section 1

Approach to the Evaluation of Peripheral Neuropathies

The process of evaluating a peripheral neuropathy can be divided into five elements: the first is having in mind an understanding of the anatomical arrangement of the peripheral nervous system; the second is having in mind the spectrum of pathologic processes that can affect nerves; the third is using an organized approach in history-taking to understand what the patient experiences, which leads to an initial formulation of the pattern of nerve involvement that is confirmed or changed based on neurologic examination abnormalities; the fourth is estimating underlying nerve pathology by electrodiagnostic or other testing; and the fifth is selecting informative laboratory tests to help determine underlying causes.

This section covers these elements, with most emphasis on the history and electrodiagnostic studies, as they define what nerve elements are involved and unlikely underlying pathology. A structured approach is efficient because it leads to a rational selection of laboratory tests. In comparison, a shotgun approach to testing is costly, with uninformative tests or false positive results. Despite a considered evaluation, an underlying cause cannot be reached in 20–30% of neuropathies (England and Asbury, 2004; Farhad et al., 2016)

References

England JD, Asbury AK. Peripheral neuropathy. *Lancet*. 2004;363:2151–61.

Farhad K, Traub R, Ruzhansky KM, Brannagan TH, III. Causes of neuropathy in patients referred as "idiopathic neuropathy." *Muscle Nerve*. 2016;53: 856–61.

Chapter 1

Peripheral Nerve Anatomy

Introduction

Peripheral nerve anatomy includes two levels: gross arrangement of nerve roots, plexuses and individual (named) nerves; and microscopic structures of nerve fibers and whole nerve structures. An understanding at both levels is a key element in localization of the site of involvement, and also in planning and interpreting electrodiagnostic studies.

Gross Anatomic Arrangement

The peripheral nervous system is composed of somatic and autonomic nerves. Somatic nerves consist of large- to medium-diameter myelinated fibers, while autonomic nerves consist of unmyelinated fibers. Somatic nerve fibers are much fewer in number compared to autonomic nerves, but most clinical symptoms and signs of peripheral neuropathies are attributable to pathology of somatic nerves (Figure 1.1). While autonomic nerves are frequently affected, symptoms are vague and signs are difficult to elicit without special autonomic laboratory testing equipment. This section focuses on somatic nerves.

Somatic Sensory Nerves

Sensory (afferent) nerve fibers are pseudo-unipolar with the cell body in the dorsal root ganglia and a peripheral process that begins with receptors in skin, joint capsule, or muscle, and a central process that terminates in the spinal cord or medulla of the brainstem (Figure 1.2). The root segment, from the cell body to entry into the cord, is important because the pathology associated with inflammatory or immune-mediated neuropathies frequently involves this segment and may cause a breakdown of the blood–nerve (root) barrier, marked by increased cerebrospinal fluid protein. Further, damage restricted to a root (such as a radiculopathy) will affect sensory perception of stimuli in a nerve's dermatome (see below), but will not affect sensory nerve conduction studies, as the peripheral segment remains connected to the cell body. Conversely, damage to nerve segments distal to the dorsal root ganglia will affect sensory perception and result in abnormal sensory nerve conduction studies. This gives rise to the terms "preganglionic" and "postganglionic" lesions.

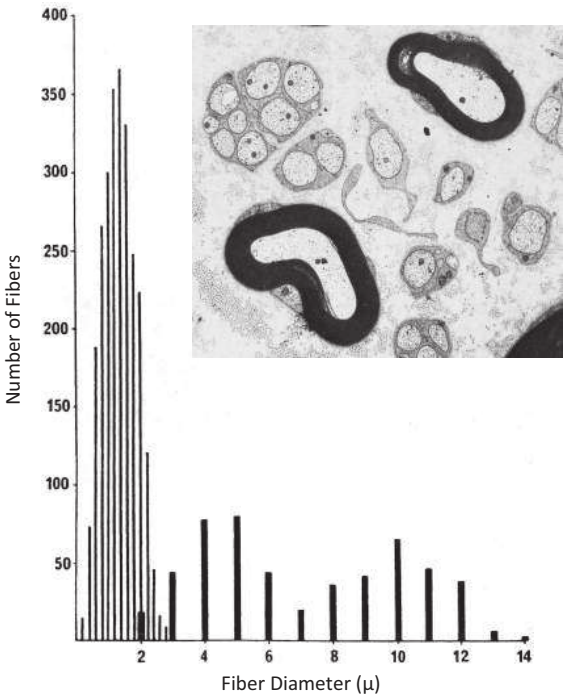

Figure 1.1 Histogram of nerve fiber diameters (μ) showing lesser numbers of large-diameter myelinated fibers (2–14 μ) compared to small-diameter myelinated and unmyelinated fibers (<1–3 μ). Inset is electron micrograph of a nerve in cross-section showing large myelinated and unmyelinated fibers.
From *Handbook of Peripheral Neuropathy*, Taylor & Francis, with permission.

Somatic Motor Nerves

Motor (efferent) nerve fibers are unipolar with the cell body in the anterior horn of the spinal cord and

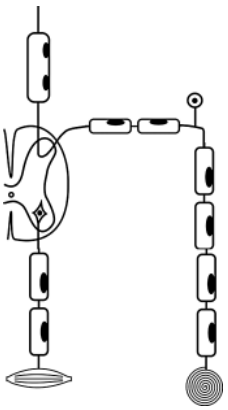

Figure 1.2 Diagram of large-diameter myelinated somatic nerve fibers. Sensory nerve fibers (right side) have cell bodies in dorsal root ganglia and begin from receptors in the skin, joint capsule, or muscle and terminate in the spinal cord. Motor nerves (left side) have cell bodies in the spinal cord and end in muscle at the neuromuscular junction.

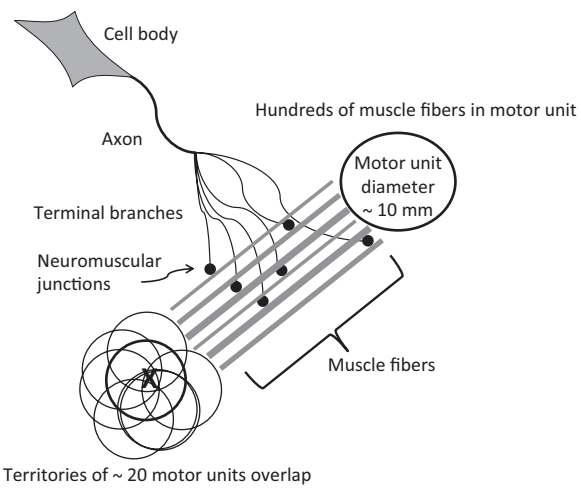

Figure 1.3 Diagram of the motor unit. The cell body is located in the spinal cord; the axon ends in terminal branches in muscle; each branch innervates a single muscle fiber at a neuromuscular junction. Each motor unit consists of hundreds of muscle fibers with a cross-sectional diameter of 5–10 mm. About 20 motor units partially overlap at any site (x) in a muscle.

a peripheral axon that terminates in muscle at neuromuscular junctions (Figure 1.2). Each motor axon branches hundreds of times within a muscle, and each terminal branch innervates a muscle fiber (Figure 1.3). Nerve action potentials are converted to muscle fiber action potentials at the neuromuscular junction, and while the process is complex, transmission is normally 100 percent secure. This functional entity is the "motor unit," consisting of the alpha motor neuron, axon, and all innervated muscle fibers.

Nerve Roots and Plexuses

At intervals along the spinal cord, sensory (dorsal) rootlets and motor (ventral) rootlets periodically join as dorsal and ventral roots, and both roots come together within the dural space to form spinal nerves, which pass through the dura (dorsal root ganglia lie outside of the dura). The spinal nerves then come together to form the plexuses. In the cervical region, nerve roots from segments C5–T1 contribute to the brachial plexus; in the thoracic region, nerve roots from segments T2–L1 remain as roots; while in the lumbosacral region roots, L2–S4 join to form the lumbosacral plexus. Each sensory nerve root innervates an area of skin called a dermatome, and each motor nerve root innervates a portion of a muscle called a myotome. Distal to the plexuses, individual named nerves form and innervate large areas of skin and whole muscles, while in the thoracic region nerve roots remain separate to innervate truncal skin and muscle.

In the brachial plexus (Figure 1.4), the arrangement of nerve branching is: dorsal and ventral roots fuse to form spinal nerves; spinal nerves divide into posterior and anterior rami; anterior rami from C5 and C6 spinal nerves join to form the upper trunk; the spinal nerve from C7 forms the posterior trunk, and spinal nerves from C8 and T1 form the lower trunk; each trunk forms anterior and posterior divisions; three cords emerge – the lateral cord from the anterior division of the upper and middle trunks, the posterior cord from the union of the posterior divisions, and the medial cord from the anterior division of the lower trunk; and finally the terminal or named nerves, which include proximally the musculocutaneous and axillary nerves, and distally the median, ulnar, and radial nerves. There may be rostral or caudal shifts of root contributions (prefixed or postfixed, respectively), but these do not affect the arrangement of nerves in the plexus (Ferrante, 2004).

The lumbosacral plexus combines the lumbar and sacral plexuses (Figure 1.5). In the lumbar plexus, the arrangement of nerve branching is: dorsal and ventral roots form spinal nerves; spinal nerves divide into posterior and anterior rami; anterior rami from L1–L4 plus a nerve from T12 form the iliohypogastric, ilioinguinal, genitofemoral, and obturator nerves, and

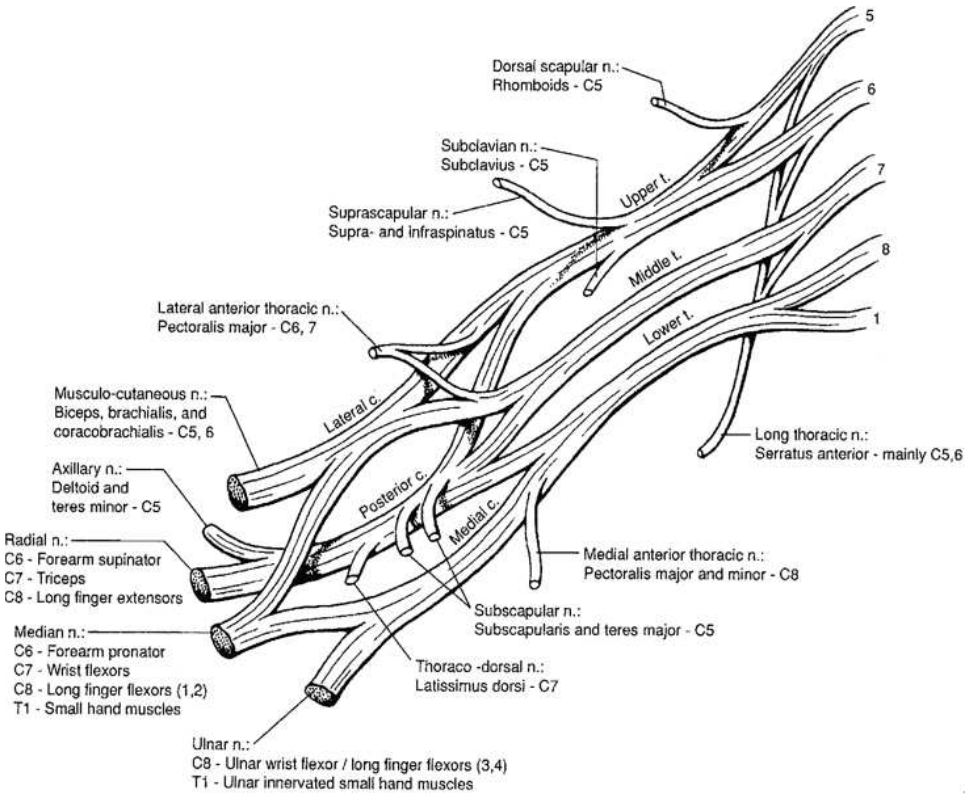

Figure 1.4 Diagram of the brachial plexus showing termination in named nerves.
From S Oh, MD, with permission.

branches from L4–L5 contribute to the sacral plexus; and posterior rami gives rise to the lateral femoral cutaneous nerve and the femoral nerve. In the sacral plexus, the arrangement of nerve branching is: the anterior rami contribute to the pudendal, levator ani nerves, the obturator nerve, and the sciatic nerve; and the posterior rami contribute to the gluteal nerves and the sciatic nerve (which includes fibular/peroneal and tibial nerves).

Peripheral Nerves

Individual named nerves emerge from the plexuses (Figures 1.4 and 1.5), and most are mixed nerves with both sensory and motor nerve fibers, and also include autonomic fibers. Cutaneous sensory nerves are branches joining mixed nerves, usually from distal areas of skin, but some join at proximal sites (cutaneous sensory branches in the forearm and leg). Motor nerves branch to muscles, and contain both motor and muscle afferent nerve fibers (from muscle spindles and tendon organs), in an approximate 50 percent:50 percent ratio. Thus, the term "motor branch" is technically inaccurate, but clinical deficits that result from motor nerve injuries primarily relate to loss of motor nerve fibers, and it is not possible to accurately gauge changes in function due to loss of muscle-afferent nerve fibers.

Nerve Variability

Dermatomes and myotomes are reasonably consistent among individuals and serve as the basis of localization of lesions. For individual dermatomes, boundaries overlap with adjacent dermatomes and published dermatomal maps may vary, and thus the effects of sensory nerve lesions may not conform to maps. Most myotomes include innervation of several muscles, and conversely, most muscles receive innervation from several roots. Further, there may be rare variability among individuals for cervical roots being shifted one root segment rostral or cauday (prefixed and postfixed plexus, respectively). Nerve fibers may follow variant (anomalous) pathways as they leave the plexus and

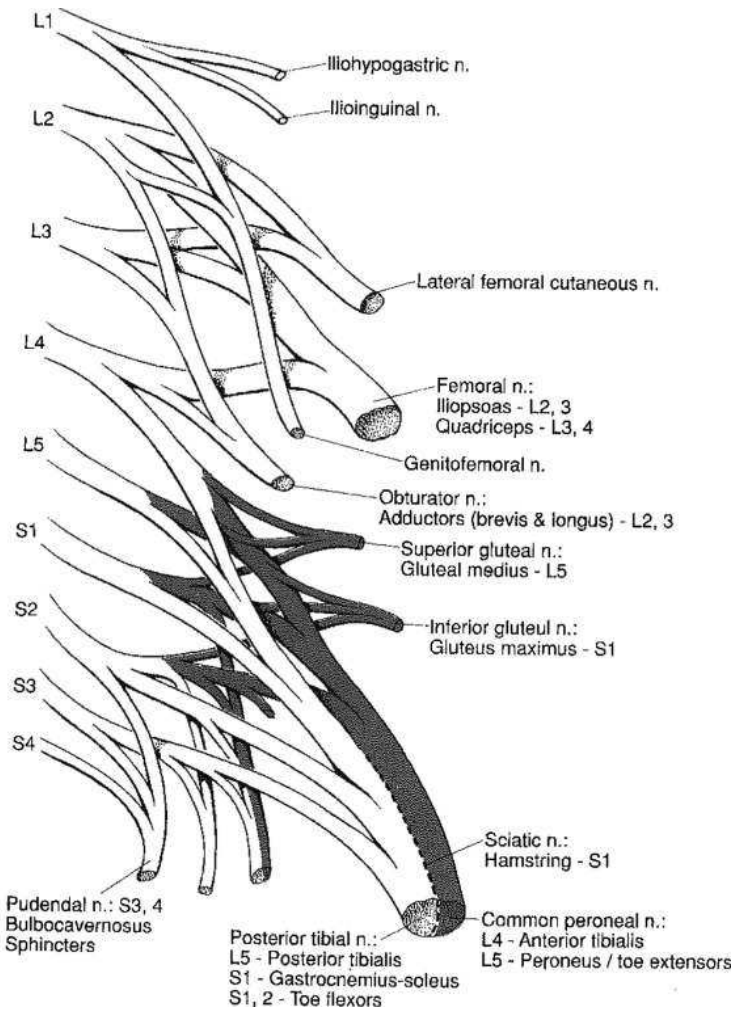

Figure 1.5 Diagram of the lumbosacral plexus showing termination in named nerves. From S Oh, MD, with permission.

move distally to muscles (most anomalies involve motor fibers). Several variants are common and can influence interpretation of electrodiagnostic studies (Gutmann, 1993; Oh, 2003). There are also rare variant muscle innervation patterns where a different nerve innervates a muscle.

Martin-Gruber Anastomosis

The Martin-Gruber anastomosis is the most common variant (15–31 percent of individuals), and involves variable numbers of ulnar motor axons initially descending with the median nerve and crossing to join the ulnar nerve in the forearm (crossings of sensory nerve fibers is rare). Several patterns are described:

- Type I involves ulnar axons crossing over from the median nerve in the forearm with normal termination in muscles in the hand, demonstrated by a lower hypothenar CMAP to stimulation of the ulnar nerve at the elbow than at the wrist. The loss of proximal CMAP amplitude could be mistakenly interpreted as conduction block in the forearm.
- Type II involves ulnar fibers to the first dorsal interosseous muscle crossing over from the median nerve in the forearm, demonstrated by a larger amplitude first dorsal interosseous CMAP to ulnar nerve stimulation at the wrist than at the elbow. This is the most common type, but does not cause confusion during routing nerve

conduction studies, which are recorded from hypothenar muscles.

- Type III involves crossings of ulnar fibers to the thenar muscles in the forearm. It is apparent when the thenar CMAP to stimulation at the elbow is greater than to stimulation at the wrist. This variant is the least common, but in the setting of carpal tunnel syndrome can lead to a very fast median forearm conduction velocity despite a prolonged distal latency (see Chapter 8).

Accessory Fibular/Peroneal Nerve

Innervation of the extensor digitorum brevis muscle is usually by the deep fibular/peroneal nerve, but a common variant (20 percent of individuals) is for a portion of the muscle to be innervated by an accessory fibular/peroneal nerve, a branch of the superficial fibular/peroneal nerve that leaves the common fibular/peroneal nerve near the fibular head and travels posterior to the deep fibular/peroneal nerve. This pattern affects nerve conduction studies and could be mistakenly interpreted as conduction block in the middle of the leg (see Chapter 11).

Variant Innervation Patterns

Rare variants include median fibers crossing from the ulnar nerve in the forearm and variations in innervation of intrinsic hand muscles (called Riche-Cannieu anastomoses). These include all thenar muscles innervated by the median nerve or all hypothenar muscles innervated by the median nerve.

Microscopic Anatomic Arrangement

Axons

Axons are the electrical conducting elements. While they are viewed as cylinders of axoplasma, they are not uniform in diameter and are narrower at specialized regions, nodes of Ranvier, and also taper over their length (Figure 1.6). The axon membrane has ion channels distributed in varying proportions along its length, in high concentrations at the nodes. Metabolic maintenance of the axon is dependent upon processes in the cell body, and it is to be appreciated that axonal processes can be very long – up to a meter in length. Disease processes that "tax" these processes likely account for the length-dependent pattern of many neuropathies. Axons do not function independent of myelin, and axon and myelin must be considered as a functional unit. Thus, neuropathies that affect myelin may secondarily affect the axon, and vice versa.

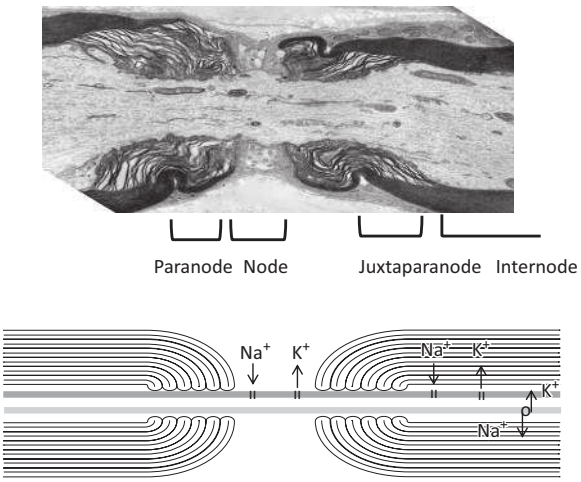

Figure 1.6 Composite picture showing structural elements at the node of Ranvier and adjacent regions. Top: micrograph of node and paranodal region. Middle: distribution of node, paranodal, juxtaparanodal, and internodal regions. Lower: distribution of sodium and potassium channels (Na^+ represents sodium transient persistent current channels; K^+ represents potassium slow fast current channels) and sodium (Na^+)/potassium (K^+) pump.

Myelin

Somatic nerve axons are individually myelinated, while unmyelinated axons are myelinated in groups, called Remak bundles (Figure 1.1). Myelin represents the extended membrane of Schwann cells, and many Schwann cells are distributed along the axon. For myelinated axons, compact myelin is tightly wrapped around the axon in Schwann cell segments, with the length of myelin covering proportional to axon diameter (segments 0.5–1.4 mm long for axons 0.5–1.4 microns in diameter). Nerve fiber action potentials are regenerated at nodes of Ranvier, and longer myelinated segments of larger-diameter nerves account for their faster conduction velocities.

Node of Ranvier

The nodal region includes the juxtaparanodal and paranodal segments (Figure 1.6). Compact myelin changes at the node of Ranvier as it clinches tightly around the axon, and the axon becomes reduced in diameter at the paranode and the node. The types and distributions of ion channels vary, with more voltage-gaited sodium channels at the nodal region and more

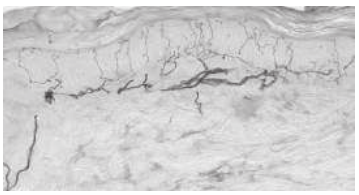

Figure 1.7 Normal pattern of unmyelinated fibers in the intraepidermal region of skin.
From University of Utah Cutaneous Pathology Laboratory, with permission.

voltage-gaited potassium channels in the paranodal region, and there are differences between fast and slow ion channels. There are also many proteins at the node that are essential for axon-myelin structure and function. The proteins can serve as epitopes for antibody-mediated immune attacks at the node (see Chapter 2).

Fascicules

Nerve fibers are organized in bundles (fascicles) within nerves. Nerve fibers can cross from one fascicule to another or stay relatively localized within a fascicle, and both patterns occur. What is important is that there is a somatotopic organization of sensory and motor nerves, especially over distal portions of nerves (Stewart, 2003). A clinical implication for an intrinsic fascicular organization is that a lesion at a proximal site affecting a fascicule can result in sensory and motor deficits in a restricted distribution of skin or muscle that can appear to result from a more distal lesion site. Specific examples are discussed in appropriate chapters.

Endoneurium, Perineurium, Epineurium

The endoneurium is a sheath around myelinated fibers and contains fibrous connective tissue and collagen. Bundles of endoneurium are in turn covered in by perineurium, which forms the fascicles. Groups of fascicles are surrounded by epineurium. Blood vessels penetrate the epineurium and then the perineurium, and capillaries lie within the endoneurium. Increased amounts of endoneurial fluid represent the basis for bright signals on magnetic resonance neurography.

Motor Unit

A motor unit consists of all muscle fibers innervated by a motor axon. An accurate number of muscle fibers included in a motor unit cannot be assessed in human muscle, but from animal experiments the number is found to be in the hundreds, and likely varies among muscles. The territory of a motor unit in a muscle is 5–10 mm across, and thus the territories of 10–15 motor units may overlap at any cross-sectional site in a muscle, with muscle fibers of one motor unit intermingled with fibers from other motor units (Figure 1.3).

Intraepidermal Nerve Terminals

Neuropathies can include damage or loss of small myelinated and unmyelinated nerve fibers. Loss of these fibers cannot be detected in the SNAP, but can be assessed on nerve biopsies, and the density of terminal branches of unmyelinated fibers in the skin can be determined in skin biopsies. Skin biopsies can be obtained from either 3-mm punch samples or skin blister preparations. Intraepidermal nerve terminal branches can be observed by staining with pan-axonal marker protein gene product 9.5 (PGP 9.5). Biopsies are customarily taken from ankle and thigh levels, where normative values are available for comparisons. The normal arrangement in skin is an orderly array of uniform diameter fibers with simple branching (Figure 1.7), whereas pathologic changes are reduced density and focal areas of swelling (Figure 2.6; Figure 1.7). Criteria for the preparation and interpretation of skin biopsies are available (EFNS, 2010).

References

European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *J Peripher Nerv Syst*. 2010;15:79–92.

Ferrante MA. Brachial plexopathies: classification, causes, and consequences. *Muscle Nerve*. 2004;30:547–68.

Gutmann L. AAEM minimonograph #2: important anomalous innervations of the extremities. *Muscle Nerve*. 1993;16:339–47.

Oh SJ. *Clinical Electromyography: Nerve Conduction Studies*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2003.

Stewart JD. Peripheral nerve fascicles: anatomy and clinical relevance. *Muscle Nerve*. 2003;28:525–41.

Chapter 2

Peripheral Nerve Pathology

Introduction

Peripheral nerve pathology can present clinically as nerve dysfunction (negative symptoms and signs) with loss of sensory perception and weakness due to disconnection from receptors or muscle fibers, or as hyperfunction (positive symptoms) with pain and other disagreeable sensations from sensory fibers, or fasciculations and cramps due to spontaneous or exaggerated motor nerve discharges. Nerve pathology can occur at the nerve cell body or anywhere along a nerve fiber. Within the body, the distribution can be in individual named nerves, multiple individual nerves, mixed sensory and motor nerves, or sensory only and motor only nerves. Underlying pathologic processes are determined from limited numbers of cases (nerve biopsy, postmortem examination with death usually from other causes) or from experimental animal models. It is important to appreciate that the role of electrophysiologic studies is to "estimate" underlying pathology, but in the absence of tissue pathology can only be inferred. However, the distribution of pathology along a nerve means that biopsy of a distal nerve segment may not include clinically relevant sites.

Nerve Damage

Causes of nerve pathology include direct and indirect trauma, biochemical insults (toxic or metabolic), or immune-mediated damage. Nerve trauma can be classified by degrees: (1) neurapraxia indicates inability to propagate a signal but the nerve is structurally intact; (2) axonotmesis indicates damage to the axon but surrounding connective tissue is intact; (3) neurotmesis indicates separation of axon and connective tissue with complete structural disruption (Campbell, 2008; Robinson, 2015). Nerve damage from trauma depends upon the nature of physical forces, and can occur focally or anywhere along a nerve. Toxic or metabolic insults can affect the cell body, causing death of the whole axon, or tax cellular metabolic processes affecting longer nerves initially and progressively shorter nerves over time. Immune-mediated damage can affect the cell body, multiple sites along a nerve or among fibers, or at the node of Ranvier.

Axonal Damage

After axonotmesis and neurotmesis, degeneration of distal axons begins within 24–36 hours after injury, but within this time period distal portions of nerve remain electrically excitable (Chaudhry and Cornblath, 1992). Regeneration at nerve ends occurs spontaneously after biochemical or traumatic injury, and involves many protein elements (Chen et al., 2007). Nerve growth cones emerge from the proximal segment and grow distally. This appears in nerve biopsies as clusters of thinly myelinated regenerating axons (Figure 2.1). With intact endoneurium, advancing axons have a chance to reach target tissue. With greater nerve disruption (neurotmesis), the degree of successful reinnervation depends on tissue obstacles (scar tissue) and the extent of the gap (if present) that the nerve fiber has to traverse, and aberrant sprouts may enter functionally unrelated endoneurial tubes or lead to neuromas (tangles of nerve endings). Under the best of circumstances, nerve regeneration advances 1–2 mm/day, and is more rapid in proximal segments and in younger individuals. In general, after severe axonal loss, any functional reinnervation will occur within 18–24 months (Robinson, 2015).

Myelin Damage

Myelin is formed from the Schwann cell membrane, and, with nerve injury, Schwann cells lose contact with degenerating axons, and dedifferentiate and proliferate (Chen et al., 2007; Gaudet et al., 2011). The Schwann cell myelin membrane breaks up into small

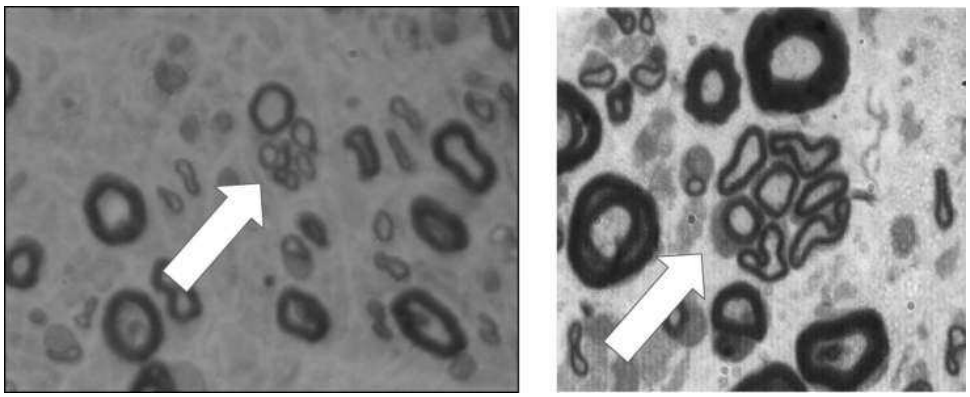

Figure 2.1 Nerve biopsy cross-sections showing clusters of regenerating nerves (white arrows). Photomicrographs from Y. Harati, MD, with permission.

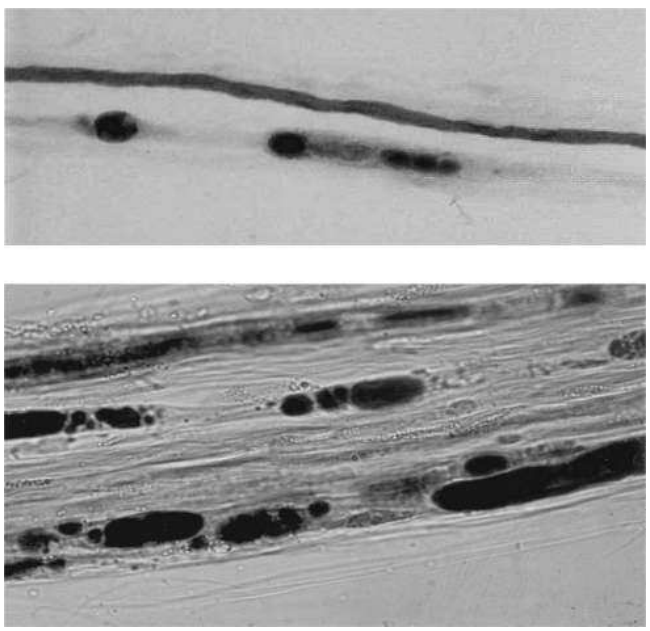

Figure 2.2 Nerve biopsies showing myelin ovoids. Upper panel is teased fiber preparation showing normal fiber above and fiber with myelin ovoids below. Lower panel is longitudinal section showing several fibers with myelin ovoids.
Photomicrographs from Y. Harati, MD, with permission.

ovoids, which participate in autophagocytosis, and Schwann cells serve as phagocytic cells (Figure 2.2). Macrophages also participate in phagocytosis. Schwann cells secrete factors that promote nerve growth, but the effect diminishes after two months. When contact is reestablished with the axon, Schwann cells redifferentiate and remyelinate the axon, but the myelin is thinner and the intermodal length reduced, resulting in slower saltatory conduction, and, as a consequence, conduction velocities are permanently slowed.

Nodal Damage

Pathology specific to the node of Ranvier is also referred to as nodopathies (Uncini and Kuwabara, 2015). Proteins at the nodes can be immunologic target sites in immune-mediated neuropathies causing nodal conduction block with relatively little structural damage (Figure 2.3). Alternatively, focal axonal damage can occur at the node.

Painful neuropathies are felt to result from alterations in ion channels, and are called channelopathies.