1 Nerve Compression, Nerve Injury, and Nerve Regeneration: An Overview

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1.1 Peripheral Nerve Anatomy and Physiology

The architecture of a peripheral nerve includes axons and perineural Schwann cells enveloped within a connective tissue matrix. Axons can be myelinated or unmyelinated and are somatotopically grouped within a peripheral nerve into units called fascicles [1]. The connective tissue framework of the nerve includes endoneurium that surrounds individual axon fibers within fascicles, a perineurium surrounding individual fascicles, and an epineurium which encircles groups of fascicles and forms the external sheath of a nerve. Within this connective tissue framework is a vascular supply that nourishes the nerve. A detailed understanding of neural anatomy and physiology provides the basis for our understanding of various mechanisms and patterns of nerve injury as well as potential for recovery. Figure 1.1 provides an overview of this architecture; each individual component is discussed in greater detail below.

1.1.1 Axon

The axon is the basic functional unit of a nerve, and a peripheral nerve can be conceptualized as a cable of axon fibers. Most major peripheral nerves contain a combination of motor, sensory, and autonomic axons. Neuronal cell bodies of motor axons are found in the ventral horn of the spinal cord, whereas sensory and autonomic cell bodies are found adjacent to the spinal cord in dorsal root ganglia and autonomic ganglia, respectively (Fig. 1.2).

Axons are long, thin processes that extend peripherally from neuron cell bodies and transmit information that is encoded in the form of bursts of electrical activity known as action potentials. The axon itself consists of an axolemmal cell membrane that houses a fluid axoplasm, a network of neurofibrils used for axoplasmic transport, and other cellular organelles. Motor axons carry efferent information from the central nervous system (CNS) to end effectors such as skeletal muscles, and sensory axons carry afferent information from sensory end organs back to the CNS. Anterograde and retrograde axoplasmic transport are energy-requiring processes that are responsible for the shuttling of materials to and from the cell body, which can be disrupted with axonal injury. An important component of this includes anterograde transport of neurotransmitter filled vesicles to the neuromuscular junction.

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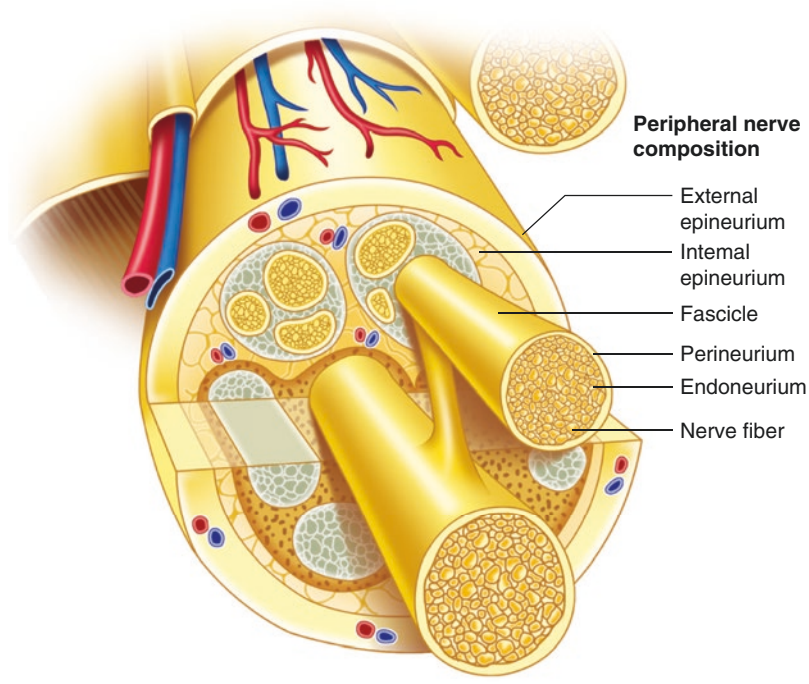

Fig. 1.1 Peripheral nerve architecture. Myelinated and unmyelinated axon fibers are surrounded by endoneurium and grouped together into fascicles by perineurium. Fascicles within the nerve are surrounded by an inner epineurium, and the entire nerve is enveloped by the outer epineurium. Longitudinal extrinsic blood vessels on the epineurial surface communicate with an intrinsic vascular plexus within the inner connective tissue framework of the nerve

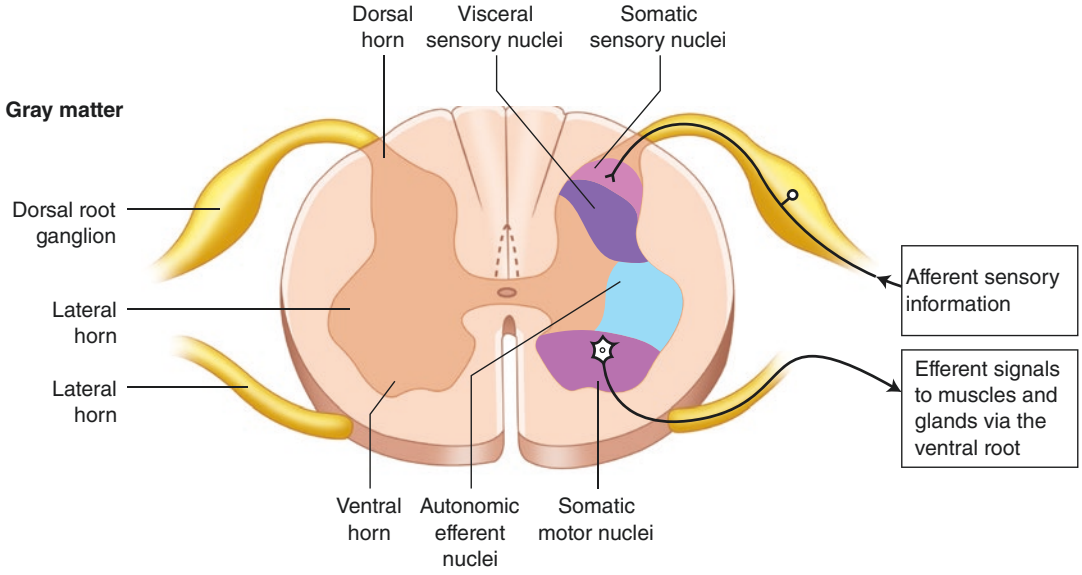

Fig. 1.2 Cross-sectional anatomy of the spinal cord. Motor cell bodies are located in the ventral horn of the spinal cord and send efferent motor axons distally. Afferent sensory information is carried from end organs proximally to bipolar sensory nerve cell bodies located in dorsal root ganglia, adjacent to the spinal cord. These bipolar sensory axons form a second synapse with sensory cell bodies in the dorsal horn of the spinal cord. Distal to the dorsal root ganglia, the motor efferent fibers and sensory afferent fibers join together into spinal nerves. Spinal nerves then branch into dorsal and ventral rami

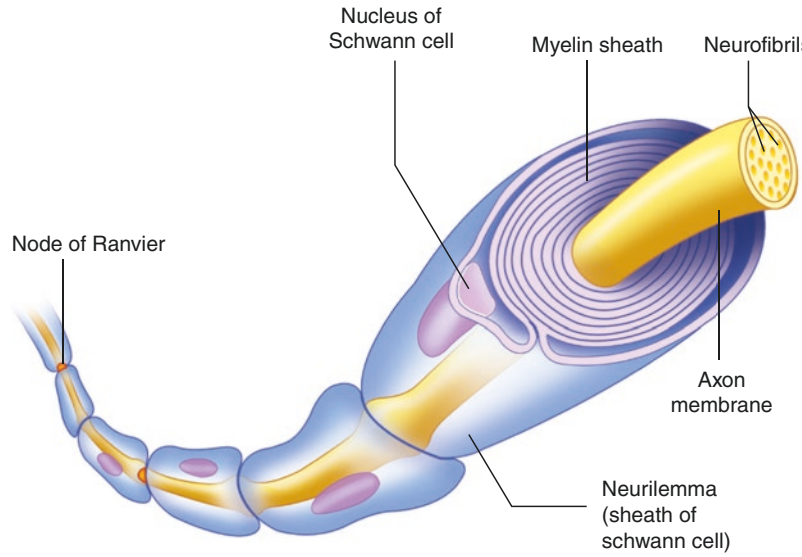

Fig. 1.3 Myelinated axon. Myelinated axon fibers are enveloped by concentric rings of myelin produced by a single Schwann cell. Myelin sheaths from adjacent Schwann cells are arranged in parallel and separated by spaces called Nodes of Ranvier. Myelin serves to insulate nerve impulses and results in "saltatory conduction," by which impulses travel quickly across myelinated sections to the Nodes of Ranvier

Axon fibers vary in diameter and in whether or not they are encased in a myelin sheath. The speed with which electric impulses are transmitted down an axon increases with fiber diameter and with myelination. Myelinated fibers are larger in diameter and are surrounded by concentric rings of myelin produced by a single Schwann cell (Fig. 1.3). Unmyelinated fibers are relatively small in comparison, averaging on the order of 1 micron. Based on these characteristics, axon fibers are classified into three broad types according to their size and speed: Groups A (motor, light touch, and proprioception fibers), B (sympathetic preganglionic motor fibers), and C (pain and temperature fibers). Group A has multiple subtypes, ranging in speed from 10 m/s (sharp pain) to 100 m/s (large motor), depending on their specific function [2].

Myelin forms a multilaminar sheath around the axon fiber composed of proteins and phospholipids produced by a single Schwann cell. Sodium channels cluster in the interspaces between Schwann cells along the length of the axon known as Nodes of Ranvier, and the electrical impulse is transmitted quickly across insulated segments between these nodes in a process referred to as saltatory conduction. In this way, myelination speeds up axon potential propagation by several fold. The conduction velocity of unmyelinated axons range from 0.5 to 10 meters per second, while myelination results in a 15 fold increase to speeds of up to 150 meters per second [3].

1.1.2 Connective Tissue Framework

The connective tissue of a peripheral nerve can be thought of as a series of tubes within larger tubes. The endoneurium immediately surrounds both myelinated and unmyelinated axons within a fascicle. It forms a continuous sheath composed of an outer layer of collagen that runs the entire length of the axon from cell body to end organ. Within this endoneurial tube, the axon is bathed in a low-protein endoneurial fluid that is analogous to cerebrospinal fluid in the CNS [4]. Fibroblasts produce collagen fibers and glycosaminoglycans within the endoneurial space and are seen to hypertrophy when a nerve is recovering from injury. Endoneurial blood vessels provide nutrient flow. The non-fenestrated endothelial cells of these endoneurial vessels are connected by tight junctions that control free diffusion of molecules into the endoneurium, thus forming a blood–nerve barrier. Endoneurial pericytes play a role in modulating this barrier, which is often disrupted after nerve injury.

Axons, with their surrounding endoneurium, are grouped together into fascicles by the peri-

neurium. The perineurium is a lamellar structure of elongated, flat perineurial cells connected to each other by tight junctions and serves as the main diffusion barrier between the endoneurium and external environment [5]. The perineurial barrier allows selective transport and vesicular transport of substances into and out of the endoneurial environment, while limiting passive diffusion. The number of perineurial cell layers increases with the size and number of axons within a fascicle, generally thinning as fascicles branch peripherally. The perineurium houses an extracellular matrix composed of collagen and fibronectin that provide a structural framework to modulate compressive forces and endoneurial pressure, thus maintaining endoneurial homeostasis.

Fascicles are themselves grouped together by the epineurium. An inner epineurium immediately surrounds the fascicles, while an outer epineurium composed of collagen and elastin fibers forms the outer layer of the peripheral nerve itself. The ratio of connective tissue to neural tissue in a peripheral nerve varies along the course of the nerve, with a greater degree of connective tissue usually found in areas where the nerve is subject to strain, such as across joints [6].

1.1.3 Vascular Supply

Peripheral nerves have a rich extrinsic and intrinsic blood supply that are interconnected [7, 8]. Extrinsic blood vessels travel longitudinally along the course of the nerve on the outer surface of the epineurium. Smith describes these extrinsic, longitudinal vessels as being located within a loose, areolar connective tissue network around the nerve called the mesoneurium. Anastomotic channels called vasa nervorum connect extrinsic vessels to a rich, longitudinal vascular plexus located in the perineurium between fascicles, thus feeding the intrinsic blood supply. Further oblique branches from this perineurial plexus anastomose with the intrinsic endoneurial vasculature. Extrinsic vessels feed the intrinsic system at various points along the nerve, though the robustness of this intrinsic circulation allows long segments of a peripheral nerve to be dissected free of the extrinsic mesoneurium without the nerve becoming ischemic, such as is required for an ulnar nerve transposition at the elbow.

1.1.4 Fascicular Anatomy

Axons within the peripheral nerve are grouped together into fascicles which vary in size between nerves and along the longitudinal axis of a given peripheral nerve. Somatotopy refers to the functional clustering of nerve fibers within a fascicle [1]. Distally, peripheral nerves have a high degree of somatotopic organization with fascicles containing groups of axons destined to innervate a specific muscle or carrying sensory information from a very specific region of the skin. These fascicles can often be dissected for several centimeters proximal to their end target. As one moves proximally along the peripheral nerve, the internal topography of the nerve becomes less cable like and more plexiform, with increasing interconnections between fascicles. Despite increasing fascicular interconnections proximally, recent experimental evidence using tracer technology and advanced imaging techniques indicates that the somatotopic organization of axons is largely maintained throughout the course of the peripheral nerve [1]. This fascicular organization of the peripheral nerve can have important implications for nerve repair.

1.2 Classification of Nerve Injuries and Implications for Prognosis

Iatrogenic injury accounts for almost 20% of peripheral nerve traumatic injuries, and orthopedic surgeons are at the highest risk of causing such injuries [9]. Knowledge of the normal anatomic structure of peripheral nerves is a prerequisite to understand the pathophysiology of nerve injury, as function follows structure. Clinically,

nerve injuries may present as anything from a mild sensory impairment (resolving within days to weeks) to a more profound loss of motor function. Prognostic information may be gleaned from accurate classification of the degree of nerve injury; therefore, Seddon devised a classification system dividing injured nerves into one of three broad categories: neurapraxia, axonotmesis, and neurotmesis [10]. While this may be an intuitive system, it belies important distinctions regarding the degree of nerve injury and potential for recovery. Recognizing these limitations, a more specific classification was devised by Sunderland to better correlate the differing degrees of injury with the underlying pathology. Ranging from Grade 1, a temporary alteration in nerve function, to Grade 5, complete severance of the nerve, Sunderland's classification correlates increasing degrees of dysfunction with increasing damage to the internal architecture of the nerve (Table 1.1). Knowledge of this classification system is important for the nerve surgeon faced with treatment of a postoperative complication, as accurate characterization can provide prognostic information for the affected patient. Ninety seven per cent of patients with Grade 1 injuries (neurapraxia) regain normal function and 83% of those with Grade 5 injuries (complete transection of the nerve) achieve little or no functional recovery [11]. However, accurate determination of the degree of nerve injury is at times best determined in retrospect, based on the ultimate recovery of the patient.

Table 1.1 Sunderland Classification of Nerve Injury [12]

Grade	Neural Elements Injured	Clinical Manifestations
1	Axonal conduction alone is interrupted, without significant derangement to the surrounding neural architecture	Rapid recovery of transient sensory deficits, with or without temporary muscle paresis or paralysis
2	Disruption of axonal continuity resulting in Wallerian degeneration in the affected axons, with maintained endoneurial tubes	Partial or complete loss of sensation or motor function. Recovery of function follows described innervation patterns of muscle with complete or near complete restoration of function
3	Disruption of endoneurial tubes and their contents	Longer period of recovery compared to second degree injuries, with incomplete recovery due to intraneural fibrosis and misdirection of regenerating axons due to loss of endoneurial tubes
4	Disruption of a larger percentage of the nerve (fascicular disruption) affecting the perineurium	Severe loss of sensory or motor function with minimal spontaneous regeneration may often result in a neuroma in continuity
5	Transection of the nerve, with disruption of the epineurium	Complete loss of all function with no spontaneous regeneration, requires repair

1.2.1 Nerve Injury

As described above, the presence of Wallerian degeneration is an important distinction between a transient conduction block and a more severe injury requiring axonal regrowth. Mechanisms of possible nerve injury include compressive neuropathies, traction injuries, or some form of traumatic transection. The molecular processes and subsequent changes in neuronal physiology can vary based on the degree and duration of nerve injury.

1.2.2 Compression Injuries

Compression of a nerve decreases venous return within the nerve and leads to increased edema that correlates with the degree of compression [13]. The degree of global nerve injury depends in part on the severity of compression – 30 mmHg has demonstrated breakdown of myelin, with 80 mmHg applied over 2 hours resulting in axonal loss in a rat sciatic nerve model [13]. Similar pressure thresholds in a rabbit tibial nerve model have demonstrated venous disruption at 20 mmHg, impairment of capillary flow at 40–50 mmHg, and cessation of intraneural blood

flow at 60–80 mmHg [14]. Two hours of severe compression at 400 mmHg resulted in persistent alterations in blood flow at 3 and 7 days post-injury.

Animal studies of acute compression have shed light on the lasting physiologic effects of isolated neural trauma. Sustained acute compressive injuries, similar to that described above, have served as the basis of several early investigations in the field. Rydevik applied increasing amounts of pressure to a rabbit vagus nerve for 2 hours and found that 50 mmHg resulted in a reversible blockage of axonal transport, while 200 and 400 mmHg resulted in sustained blockage for up to 1 and 3 days. While these pressures did not induce Wallerian degeneration, the authors note that smaller unmyelinated fibers such as the vagal nerve are more resistant to injury than larger myelinated fibers [15]. A similar experiment conducted on rabbit tibial nerves showed minimal effect on nerve conduction velocity at 50 mm Hg compression. However, 200 and 400 mm Hg resulted in reduction of conduction velocity that persisted for at least 2 weeks, with evidence of axonal injury and demyelination [16]. Prior studies demonstrated that a traumatic compression of 50 mmHg for 2 hours resulted in alterations of epineurial vessels, while prolonged trauma or increased pressure resulted in endoneurial damage [17]. A clinical corollary for the surgeon is that even minor pressure or retraction to a nerve applied for a long duration during a case can result in alterations in axonal transport or even axonal damage from acute compression. The degree of dysfunction should be related to the magnitude and duration of the compressive injury.

These changes found in the epineurial and endoneurial vessels after prolonged compression help to explain the pathophysiology of chronic compression as well. The first manifestation of compressive nerve injury is edema with subsequent fibrosis of the perineurium and epineurium. Persistent intraneural pressure elevation leads to loss of myelin around the axons (Fig. 1.4) with a resultant increase in latency detectable on nerve

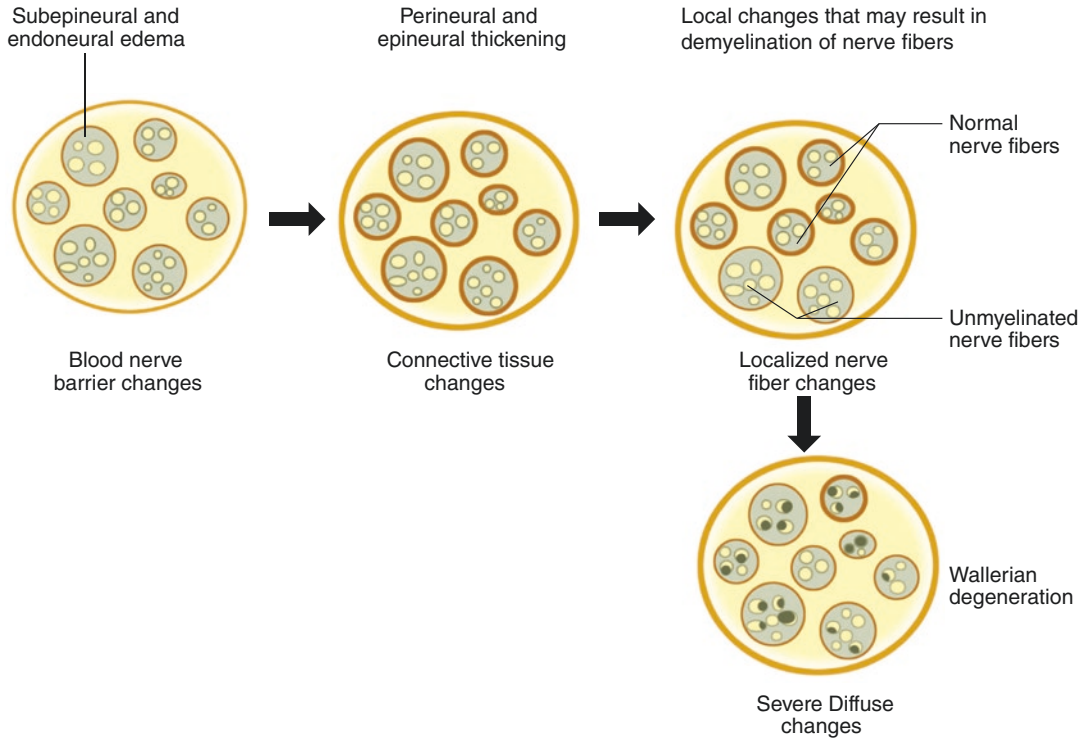

Fig. 1.4 Sequelae of nerve compression. Progressive ischemic changes occur in the peripheral nerve in response to compression, resulting ultimately in fibrosis

conduction studies (NCS). As the injury progresses, endoneurial ischemia develops, with subsequent axonal degeneration, venous congestion, and inflammation [18]. Initial treatment strategies of compressive neuropathy rely on decreasing pressure experienced by the nerve. In the most common compressive neuropathy, carpal tunnel syndrome [19] is accomplished with splints to alter wrist position or steroid injections to reduce swelling and decrease pressure in the carpal tunnel. Surgical release can substantially improve nocturnal symptoms and results in more than 80% patient satisfaction, but persistent slowing in nerve conduction studies is present in almost 80% of patients at 1 year [20].

The increased edema seen with chronic compressive neuropathies and the discomfort accompanying electrodiagnostic testing has given rise to interest in the use of ultrasound (US) to diagnose peripheral entrapment neuropathies. The overall cross-sectional area of the median nerve on ultrasound has been found to correlate with severity of carpal tunnel syndrome [21]. Beyond morphologic changes, intraneural blood flow has been identified as a possible predictor of median nerve entrapment at the wrist. A critical review of studies using Doppler sonography to identify carpal tunnel syndrome reported a median sensitivity of 72% and a median specificity of 88% [22]. A meta-analysis performed by Fowler et al. evaluating ultrasound findings of structural changes yielded similar findings, with a diagnostic sensitivity of 77.6% and specificity of 86.8% [23].

While the electrophysiologic changes associated with carpal tunnel release are well studied [24], less is known about the natural history of the above morphologic changes to the nerve. Li et al. examined the changes in median nerve cross-sectional area and total length of nerve edema before and after carpal tunnel release. They found that a significant improvement in cross-sectional area and nerve diameter was seen between 4 and 12 weeks postoperatively; however, a return to normal nerve diameter was not seen until 1 year after surgery. Even at 1 year follow-up, cross-sectional area was marginally increased compared to healthy controls [25].

1.2.3 Stretch Injury

Uninjured peripheral nerves have the capacity to glide within the extremities – this has been measured at almost 20 mm for the median nerve at the wrist [26]. Animal studies have shown acute changes in nerve conduction with increasing stretch of nerves – Wall demonstrated a transient 70% decline in conduction amplitude after a 6% strain on a rabbit tibial nerve for 20 minutes. When the strain was increased to 12%, a complete conduction block was found, with only a 40% recovery at 2 hours post-injury [27]. Kwan further investigated the ex vivo mechanical properties of rabbit tibial nerve, as well as in vivo responses to stress and strain in the rabbit tibial and sciatic nerve. Ex vivo testing of the tibial nerve resulted in a stress/strain curve demonstrating significant intrinsic strain in vivo with minimal stress. The viscoelastic behavior of the nerve allowed stress relaxation under mild strains, but failure of the nerve under high tension occurred due to perineurial disruption, beginning at a 27% increase beyond in situ strain. Nerve conduction velocity was maintained at 60% of normal amplitude after an hour of 6% strain, but dropped to 40% of normal within 20 minutes of application of a 12% strain [28].

Laser Doppler flowmetry has been used to better characterize the physiologic mechanisms contributing to decreased neural function under stress and strain. Peak conduction velocity and blood flow were measured under conditions of increasing strain in a rabbit tibial nerve. While an 8% and 16% strain both resulted in similar reductions in blood flow, only the 16% strain caused a drop in peak conduction velocity, leading the authors to conclude that ischemia alone cannot explain changes in nerve function due to significant strain [29].

1.2.4 Nerve Transection/Severe Axonotmetic Injury

While the peripheral nervous system has a capacity for axonal regeneration, particularly in compressive neuropathies or mild stretch injuries, the

repair of a transected nerve yields inferior outcomes compared to the native state. This is likely due to derangement of the internal architecture and resultant misdirection of recovering axons. Maximal return of motor strength may not occur for up to 4 years [30] as collateral sprouting occurs and the nerve must regenerate to its target from the site of injury. Recovery of nerve function and growth is estimated as 1 mm/day or 1 inch per month in humans and typically regarded as 2–3.5 mm/day after transection in rats and rabbits [31]. Therefore, nerve injuries occurring near the shoulder may take more than a year to reach target muscles in the hand. This poor return of function and lengthy time to achieve some recovery has profound consequences on the emotional and financial well-being of the patient. Indirect costs alone from lost wages after traumatic brachial plexus injuries of the upper extremity have been estimated at more than $1.1 million [32]. Therefore, maximizing functional recovery by early and accurate diagnosis and subsequent intervention is paramount for the treating surgeon. A basic understanding of the pathophysiologic processes of nerve injury, degeneration, and repair by nerve surgeons is therefore critical to help inform clinical decision making.

1.2.5 NAD+ Homeostasis Is Critical to Preserving Distal Axonal Integrity

Upon transection or severe injury of a nerve, a complex interplay of irreversible changes occurs, beginning within 6 hours of injury. Initial extracellular calcium levels rise in the proximal and distal stumps, which leads to a series of molecular events that consume nicotinamide adenine dinucleotide (NAD+), increase levels of nicotinamide mononucleotide (NMN), and reduce levels of ATP [33]. In uninjured nerves, NAD^+ is present in higher concentrations than NMN. NAD^+ is generated by nicotinamide mononucleotide adenyltransferase 1 (Nmnat1) utilizing NMN as a precursor. The loss of ATP from the axons leads to dysfunction of its normal energy balance, resulting in mitochondrial destabilization and release of intracellular calcium from mitochondrial stores [33]. This second release of calcium appears to be critical for axonal degradation and initiation of Wallerian degeneration, resulting in destabilization of microtubules as well as fragmentation of axons, with their subsequent clearance by glial cells.

The onset of Wallerian degeneration stimulates Schwann cell transdifferentiation from a pro-myelinating phenotype into a regenerative phenotype critical to the process of neuronal regrowth. This Schwann cell transdifferentiation occurs due to upregulation of the transcriptional factor c-Jun [34] after nerve injury, due to increased intracellular Ca^{2+} levels [35]. C-Jun is critical to the formation of Bands of Bungner and promotion of axonal regeneration across the repair site [36]. Macrophages also appear to have a role in the regulation of Schwann cell response to nerve injury, assisting in proliferation of mature Schwann cells from a regenerative phenotype to a remyelination phenotype (transdifferentiation), likely via Gas6 [37], as part of the overall inflammatory process leading from nerve injury to nerve repair. The transcription factor Krox-20 functions to inhibit c-Jun activation, serving as a negative control to promote differentiation of Schwann cells back into the myelinating phenotype [38].

SARM-1 has been identified as the central executioner of Wallerian degeneration by cleavage of NAD^+ through the intrinsic NADase activity housed in its Toll/Interleukin-1 Receptor [39] (TIR) domain, which results in an imbalance of NMN vs NAD+. The importance of the relative balance of NMN and NAD+ to neuronal homeostasis has been underscored by the finding that the Wld^s protein prevents or delay axonal degeneration, through synthesis of NAD^+ with its nicotinamide mononucleotide adenyltransferase 1 (Nmnat1) enzymatic domain [40]. Animals with this phenotype demonstrate delayed Wallerian degeneration after nerve injury, supporting the concept that loss of NAD^+ and subsequent ATP loss is critical to initiation of Wallerian degeneration. However, the exact mechanism by which SARM-1 is activated after injury is still unclear, although some reports suggest that it is related to

the intrinsic neuronal immune response to injury [41]. Loss of SARM-1 prevents consumption of NAD+ after axonal injury, resulting in conserved levels of ATP [42] and ultimately preventing calcium influx as well as Wallerian degeneration [43].

1.2.6 Assessment of Nerve Injury

Imaging can play a role in the evaluation of peripheral nerve dysfunction after surgery. No clear consensus exists on the ideal imaging method, but both ultrasound (US) and magnetic resonance imaging (MRI) have proven to be effective. MRI relies on detecting the difference in proton concentrations between tissues – therefore, pathologic conditions that result in increased edema or proton shifts may be amenable to evaluation with MRI. Increased T2 signal within a rat sciatic nerve after axonotmetic injury has been correlated with nerve conduction changes and muscle strength. An increase in signal distal to the site of the injury was visualized immediately, and this signal persisted until 2 weeks prior to complete restoration of compound motor action potentials (CMAP) in the foot. A proximal to distal resolution of the edema correlated well with functional recovery at the affected level [44]. Cudlip demonstrated similar increases in T2 signal intensity after a crush injury with a forceps, as well as a transient increase in sham-operated controls [45]. A more recent retrospective clinical series correlated intraoperative findings of a neuroma with preoperative MRI findings. All 20 neuromas in this series showed indistinct margins, and the portion of the nerve distal to the injury was larger in diameter than the more proximal nerve [46].

Traditional MRI has given way in recent years to magnetic resonance neurography, a specific technique utilizing MRI but focused on visualization of peripheral nerves. The precise spatial resolution of MR neurography (0.3–0.5 mm) allows detection of changes in a myriad of nerve properties to more precisely identify and characterize peripheral nerve pathology [47]. The characteristics that can be evaluated include changes in nerve diameter, contour, fascicular arrangement, continuity, signal intensity, and fat planes. This precision is helpful in the diagnosis of peripheral nerve injuries and the distinction between neurapraxic, axonotmetic, and neurotmetic injuries, which may influence clinical decision making (Table 1.2).

Enthusiasm for the wealth of information available from MR neurography is tempered by its potential cost and lack of availability in certain centers. A less expensive and more readily accessible alternative to evaluate peripheral nerve pathology is ultrasound (Fig. 1.5). The feasibility of ultrasound in detecting peripheral nerve injuries has been demonstrated in a cadaver study of 12 arms [48]. A sonographer blinded to the location of the nerve injuries was able to accurately detect nerve transection with a sensitivity of 89% and a specificity of 95%. Small case series have shown the potential of localization of iatrogenic injuries using ultrasound by examining for diffuse axonal swelling, nerve discontinuity, and compression of nerves by overlying plates [49].

Ultrasound also allows evaluation of the surrounding tissue to assess for hematoma or scar tissue. Karabay [50] examined clinical applications of ultrasound in the diagnosis of nine patients with iatrogenic upper extremity peripheral nerve injuries over a period of 3 years. All but one of the injuries involved the radial or posterior interosseous nerve (PIN), and five of the nine were indicated for exploration of the nerve based on the ultrasound findings. In one of the patients, the nerve could not be visualized due to body habitus. The authors used the following criteria as ultrasound evidence of a nerve injury:

1. Complete lack of nerve continuity
2. Formation of a neuroma or general fusiform swelling of the nerve at the suspected site of injury
3. Loss of fascicular pattern, or in partial injuries, evidence of intact epineurium on one side and disruption of the epineurium on the other side of the nerve
4. Hypoechoic texture of the nerve on ultrasound or generalized swelling of the nerve (possible stretch or contusion injury)

Table 1.2 Nerve injury classification (grading) based on Seddon's and Sunderland's classifications, electrophysiology, and magnetic resonance neurography (MRN) findings [47]

Sunderland class of nerve injury	Seddon class of nerve injury	Myelin	Axon	Endoneurium	Perineurium	Epineurium	Electrophysiology			MRN findings
							SNAP	CMAP	EMG	
I	*Neurapraxia*	Abnormal	Normal	Normal	Normal	Normal	Normal	Normal or CB	Normal but IP Decreased	Hyperintense nerve
II III	*Axonotmesis*	Abnormal Abnormal	Abnormal Abnormal	Normal Abnormal	Normal Normal	Normal Normal	Ampl Decreased	Ampl Decreased	SA and IP Decreased	Hyperintense and thickened nerve with/without prominent fascicles
IV		Abnormal	Abnormal	Abnormal	Abnormal	Normal			0	Heterogeneous nerve signal with lateral or fusiform neuroma in continuity
V	*Neurotmesis*	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	Absent	Absent	No MUPS	Complete nerve gap

Please note muscle denervation change is typically absent in class I injury and full recovery is expected in class I/II injuries. In class III–V injuries, prognosis is guarded
SNAP sensory nerve action potential, *Ampl* amplitude, *CMAP* compound motor action potential, *EMG* electromyography, *CB* conduction block, *IP* interference pattern, *MUPS* motor unit potentials, *SA* spontaneous activity

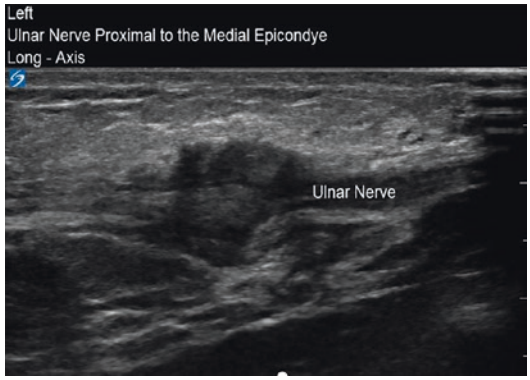

Fig. 1.5 Ultrasound of a neuroma. An ulnar nerve neuroma is imaged just proximal to the medial epicondyle – note the large bulbous structure consistent with a neuroma continuous with the normal caliber of the ulnar nerve proximally

A retrospective review comparing the sensitivity and specificity of ultrasound and MRI in identifying peripheral nerve pathology demonstrated a higher rate of true positives found in ultrasound, with a similar rate of true negatives between the modalities. Ultrasound was accurate and MRI was inaccurate in the diagnosis of 25% of patients [51]. The inaccuracy of MRI in fully identifying the peripheral nerve lesion was attributed to a more limited field of view with MRI, resulting in missed pathology outside of this field of view. The authors suggest that ultrasound is the preferred imaging modality for peripheral nerve pathology when the anatomic location is suitable for ultrasonography of nerves.

1.2.7 EMG/NCS

Despite advances in peripheral nerve imaging, nerve conduction studies and EMG remain the gold standard for diagnosis of peripheral nerve pathology. As the validity of the studies can be operator dependent, it is important for a peripheral nerve surgeon to develop a relationship with a trained electrophysiologist whom they trust to perform meticulous and accurate testing. Two types of electrophysiology tests are commonly employed – nerve conduction studies (NCS) and electromyography (EMG). NCS evaluates the health of the nerve itself, specifically the ability of the axons and myelin to propagate an electrical signal. However, NCS and EMG are only useful predictors of nerve function at a minimum of 2–3 weeks post-injury. After injury, nerves will undergo Wallerian degeneration, thus the true extent of the lesion will not be evident until this process has finished – earlier tests may give inaccurate diagnoses.

The treating nerve surgeon should have a basic understanding of the terminology and principles used in interpreting nerve conduction studies. In nerve conduction studies, stimulating electrodes are utilized to impart an electrical stimulus to the target nerve. In assessing sensory conduction, stimulating electrodes are placed over the area of sensory innervation and recording electrodes are placed proximally over the nerve to be assessed. This represents an orthodromic study, as it mimics the typical direction of a sensory nerve action potential (SNAP) propagation. Several parameters of a SNAP are of interest in identifying nerve pathology (Figs. 1.6 and 1.7). The latency of a signal refers to the elapsed time between the stimulus and the onset (or peak) of the sensory action potential. Nerve conduction velocity can be calculated by determining the latency at different locations and measuring the distance between these locations. Latency increases at further distances from the spinal cord, and changes in latency and conduction velocity reflect alterations in myelination [52]. In addition to latency, the amplitude of a signal gives critical information about the SNAP. Amplitude is a general measure of the strength of the conducted signal, which correlates to the number of axons that are functioning. In axonotmetic injuries, conduction may be possible, but with reduced amplitudes, reflecting the severity of the injury [52]. Similar to sensory nerve conduction studies, motor nerve conduction studies can be performed by placing a stimulating electrode proximally over the nerve of interest and recording the compound motor action potential (CMAP) generated by the muscle distally. CMAP latency and amplitude are measured in a method analogous to that used for SNAP latency and amplitude.

A commonly discussed phenomenon in brachial plexus injuries is that of a patient with a

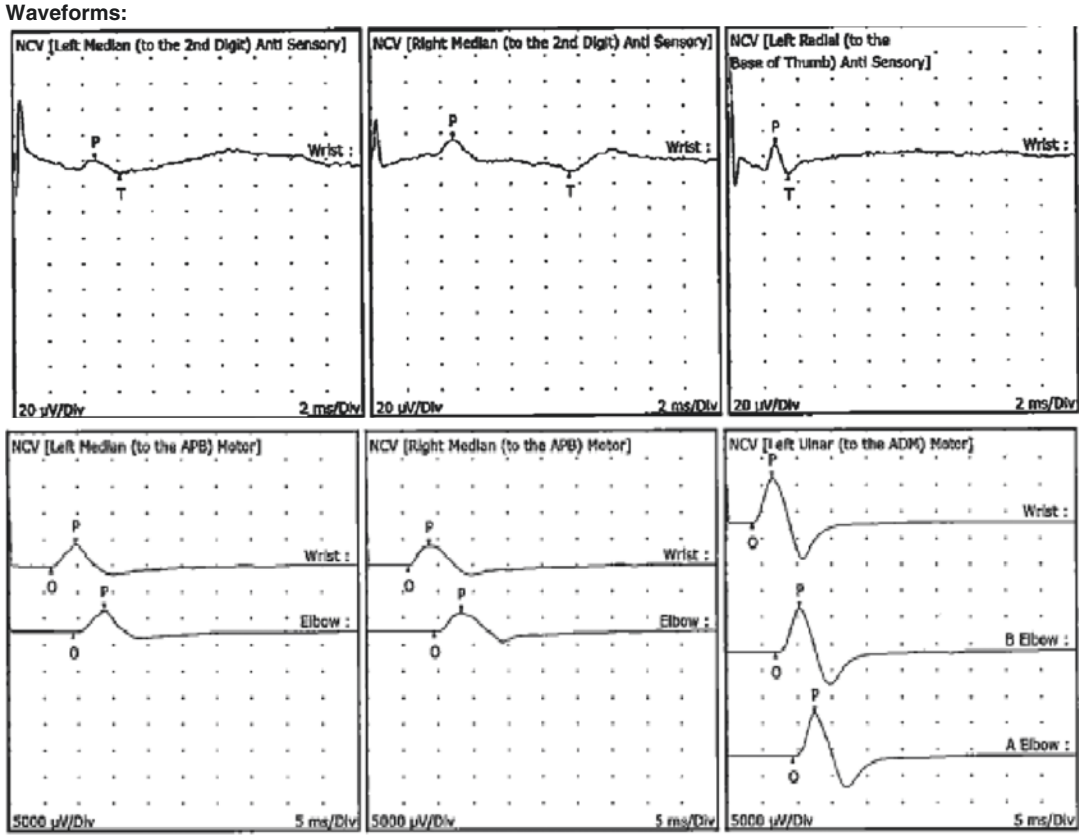

Fig. 1.6 Sensory and motor nerve conduction study waveforms. Example of sensory and motor nerve conduction studies in a patient with moderate bilateral carpal tunnel syndrome. Note the comparison of median SNAP to the radial nerve SNAP on the far right (top row). The amplitude in the left SNAP is severely reduced, latency is also increased as seen in the delay from the stimulus artifact on the far left of the waveform to the peak of the action potential. CMAP is also demonstrated for bilateral median nerves and the left ulnar nerve (bottom row) – note the reduction in CMAP amplitude on the right side compared to the left, and the increased latency of both compared to the normal ulnar nerve

severe preganglionic lesion, anesthesia throughout the extremity, no motor function, and a normal SNAP on nerve conduction tests. This constellation of signs and symptoms occurs when the connection of the sensory nerve is maintained to the dorsal root ganglion (DRG), but the spinal connection more proximally is disrupted. The SNAP appears normal as the conduction to the sensory cell body in the DRG is maintained, but this data is not transmitted to the brain. Similarly, the connection to the anterior horn cells controlling motor function is disrupted, resulting in muscle paralysis.

Electromyographic studies are commonly performed as a complement to the nerve conduction studies described above (Fig. 1.7). The focus of the electromyography is on the muscle itself by utilizing small needles placed within the muscle. A denervated muscle will display signs of electrical instability, manifesting as spontaneous fibrillation potentials, positive sharp waves, or fasciculations. These spontaneous activities begin at 2–6 weeks post-injury and continue until complete degeneration of the muscle fiber or reinnervation occurs [53]. Fasciculations are another type of increased insertional activity that

Summary													
			Insertional	Spontaneous				MUAP					Comments
Muscle	Nerve	Roots	Activity	Fib	PSW	Fase	Other	Dur	Amp	Poly	Recruit	Activate	Comments
R. Deltoid (middle)	Axillary	C5-C6	Increased	2+	3+	None	-				None	None	-
R. Biceps brachii (long head)	Musculocutaneous	C5-C6	Increased	2+	3+	None	-				None	None	-
R. Triceps brachii	Radial	C6-C8	Increased	2+	3+	None	-				None	None	-
R. Flexor carpi ulnaris	Ulnar	C7-T1	Increased	3+	3+	None	-				None	None	-
R. Extrnsor indicis proprius	Radial	C7-C8	Increased	3+	3+	None	-				None	None	-
R. Flexor carpi radialis	Median	C6-C7	Increased	3+	3+	None	-				None	None	-
R. First dorsal interosseous	Ulnar	C8-T1	Increased	3+	3+	None	-				None	Poor	-
R. Abductor pollicis brevis	Median	C8-T1	Increased	3+	3+	None	-				None	None	-
R. Supraspinatus	Suprascapular	C5-C6	Increased	3+	3+	None	-				None	None	-

Fig. 1.7 EMG after nerve injury. EMG results from a patient with a multiple root preganglionic avulsion injury to the brachial plexus 6 weeks prior to the nerve study are displayed. Note the fibrillations and sharp waves seen throughout the right upper extremity consistent with acute denervation and resulting electrical instability of the muscle. No evidence of polyphasic motor units is identified given the severity of the injury and lack of recovery

can be present in neuropathic and myelopathic disorders – they stem from spontaneous discharge of the entire muscle unit and can be found in anterior horn cell disease, myelopathy, and radiculopathy [54]. After nerve injury, polyphasic potentials may be found and can be categorized into either nascent potentials or long duration motor units from collateral sprouting. The presence of these long duration units will help to quantify the injury as subacute, as this sprouting does not occur immediately. Nascent potentials, which are usually shorter in duration, represent true axonal recovery and must be distinguished from polyphasic potentials from sprouting for prognostic purposes [55].

1.2.8 Injury Recognition and Time to Surgery

The importance of timely recognition and accurate diagnosis of peripheral nerve injuries is underscored by the fact that early repair of nerves may result in improved outcomes compared to delayed repair [56]. Atrophic changes within denervated muscles and histologic changes around the motor end plates result in worse functional outcomes after long periods of denervation [57], due in part to the need for the nerve to create new functional end plates in the atrophied muscle. Some surgeons have found the time to surgery to have such a dramatic effect on functional recovery that they have advocated for urgent brachial plexus exploration and repair within 7 days of the injury [58]. Earlier surgery could lead to earlier muscle reinnervation to minimize motor fiber changes, as well as better pain relief. In a series of 148 patients with brachial plexus injuries and at least one nerve root avulsion, Kato et al. demonstrated improved pain relief in patients undergoing surgery within 1 month of injury [59].

While the timing of surgery for brachial plexus injuries is controversial, most experts would suggest that the standard of care within the United States is to proceed with observation and surgery within 3–6 months of the injury or sooner if a plateau in recovery is evident [60, 61]. For iatrogenic nerve injuries after operation, consideration could be given to immediate re-operation if there is a high index of suspicion for any injury beyond Grade 1 or 2. When nerve injuries are recognized intraoperatively, they should be repaired primarily or within 3–4 weeks if the zone of injury is uncertain. Similarly, if postoperative US or MRI demonstrates evidence of

transection or neuroma in continuity, surgery should be performed without a significant delay [62]. Timing may be delayed secondary to limited access to peripheral nerve surgeons, as has been demonstrated in brachial plexus injuries [63]. This, coupled with failure to diagnose the nerve injury or failure to refer the patient to an experienced surgeon, can lead to unacceptable delays in a majority of patients. Ideally, peripheral nerve injuries, particularly iatrogenic injuries, are operated on within 3–4 months [62]. Despite these recommendations, only about 1/3 of patients are seen and treated within 6 months of their injury [9].

1.2.9 Nerve Repair and Regeneration

In the most severe injury, neurotmesis, nerve repair is required to approximate damaged nerve ends. An ideal nerve repair will have minimal gapping, minimal tension, appropriate fascicular alignment, and no evidence of fascicles extruded from the periphery of the repair [64]. Approximation of the nerve ends with minimal gap is critical to facilitate axonal bridging from the healthy proximal nerve to the distal degenerative nerve. Transdifferentiation of the Schwann cells into a pro-regenerative phenotype is an important component of neuronal regeneration. A growth cone consisting of filopodia responds to neurotrophic and neurite promoting factors to cross the nerve gap between the repaired ends and initiate regeneration within the distal segment [65], as shown in Fig. 1.8.

The regenerating fibers must then regrow the length of the axonal segment to the target organ at a speed of 1 mm/day [67]. Therefore, nerve transections far from the target muscles result in significant delays in recovery, accompanied by muscle wasting of 60–80% of volume 4 months after injury [65, 67].

1.3 Downstream Effects of Nerve Injury on Muscle

Distinct changes in the neuromuscular junction and muscle itself begin to occur shortly after a traumatic nerve transection. Muscle fibers begin to atrophy early after denervation, with a 70% reduction in muscle cross-sectional area by 2 months after injury [67]. This is accompanied by muscle fibrosis, characterized histologically by fibroblast proliferation and collagen deposition within the muscle. Dropout of motor fibers begins to occur between 6 and 12 months after denervation [67]. Histologic studies from both animal models and biopsies of human denervated muscle show a time-dependent condensation of motor end plates with loss of normal morphology and a significant reduction in surface area and volume [68]. Postsynaptic acetylcholine receptors on the neuromuscular junction begin to redistribute and over time are lost [69]. After 6 months of denervation, the possibility of full muscle recovery with innervation begins to decrease. By 12–18 months after denervation, the above changes in the neuromuscular junction and progressive muscle fibrosis are permanent and preclude reinnervation by regenerating axons and recovery of motor function [70].

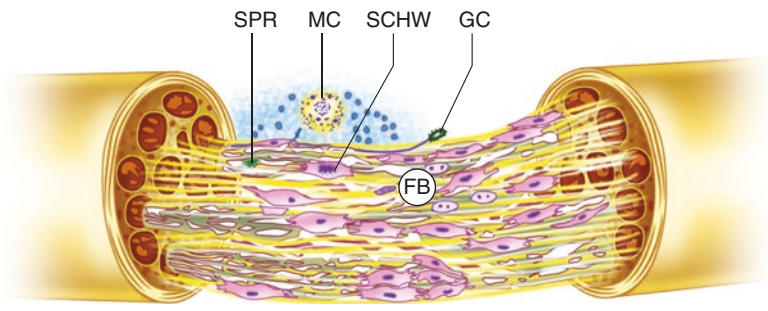

Fig. 1.8 Nerve regeneration after repair. A growth cone from the proximal nerve stump guided by neurotrophic factors bridges the gap between repaired nerve ends (SPR: Sprouts; MC: Mast Cell; SCHW: Schwann Cell; GC: Growth Cone; FB: Fibroblast). [66]

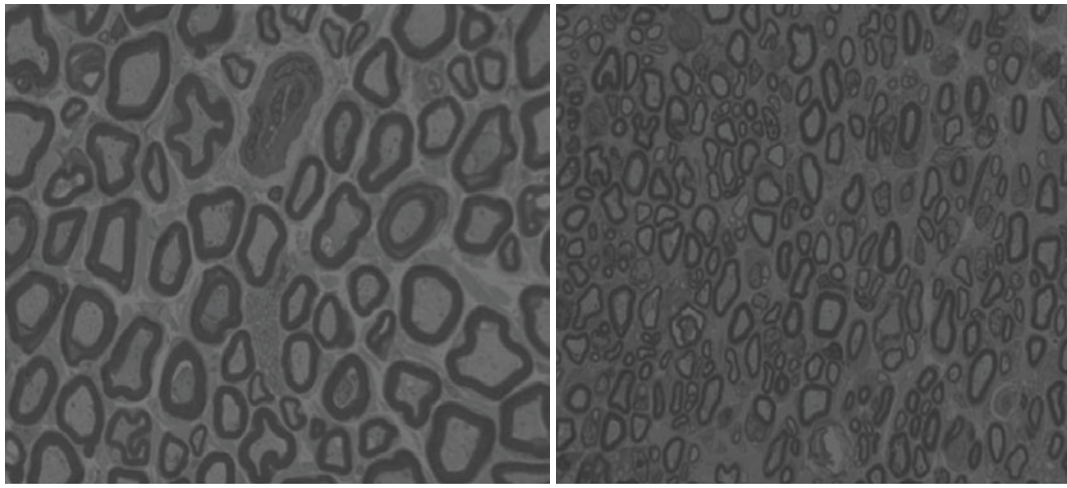

Fig. 1.9 Histology of a recovering nerve. Histologic section demonstrating normal nerve (left) and recovering nerve after transection and repair (right). Note smaller, disorganized axons and thinner myelin sheaths

Due to the downstream cascade of pathologic events, clinical results of nerve repairs are not encouraging – primary repairs of major peripheral nerves generally result in useful function (classified as good or excellent results) in less than half of patients [71] and up to a third of patients may have little or no recovery whatsoever [72], in part due to the disorganized nature of axonal recovery (Fig. 1.9). Return of normal function is almost never achieved and should not be expected; one series of iatrogenic nerve injuries showed improvement after surgery in only 70% of cases [9]. This is likely due to a combination of the delay in reinnervation due to the length of regeneration required and inefficient healing of the nerve across the transected ends. Clinically, this manifests as patients waiting for months to years to achieve any form of recovery of their paralyzed muscles, with modest success at best.

1.4 Nerve Repair Techniques

The goal of peripheral nerve repair is a tension-free coaptation that aligns fascicular topography. A great deal of work over the past 50 years has elucidated technical factors that play an important role in the success of a nerve repair. Nerve regeneration following repair is influenced by intrinsic characteristics of the injured nerve, the surrounding environment the injured nerve is placed in, and the technique with which the nerve is repaired. The surgeon must pay attention to all of these aspects of the nerve repair in order to give an injured nerve the best chance of recovery.

1.4.1 End-to-End Coaptation

The first step in performing a nerve repair is to assess the soft tissue wound bed and coverage. If needed, a flap reconstruction can be performed to provide a well-vascularized bed and coverage for the regenerating nerve. Once the wound bed is optimized, the next step is to determine the health of the injured nerve segments. Successful nerve regeneration requires unimpeded axonal sprouting from the proximal segment of a cut nerve. A severe crush injury, scar, or fibrosis of the end of the proximal nerve stump impairs axonal sprouting; therefore, scarred segments of the proximal stump must be resected prior to coaptation [73]. Evaluation of the nerve stump is primarily clinical and subjective. The nerve end is inspected for visible fascicles and is palpated. A healthy nerve is soft to the touch and compressible; in contrast, a damaged fibrotic nerve may be firm and incompressible. Bleeding from epineurial vessels is another sign of nerve health, and

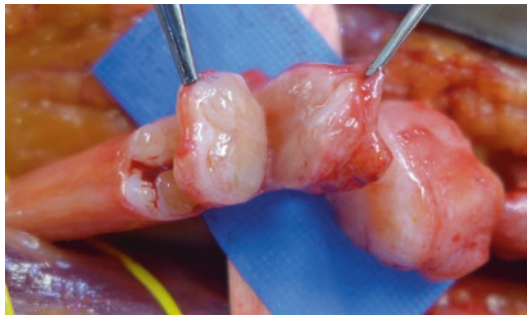

Fig. 1.10 Zone of transition within a neuroma that has been serially sectioned to reveal areas of fibrosis with increasingly healthy nerve tissue proximal to the zone of injury. Image copyright the authors and used with permission

resection of the proximal nerve stump to such a healthy level takes precedence over attempts to preserve length (Fig. 1.10). Similar considerations guide preparation of the distal nerve stump.

Once the nerve is prepared, attention must be paid to aligning fascicular groups to the extent possible. In sharp lacerations or injuries without extensive soft tissue destruction and loss, the position of the nerve stumps within their tissue bed provides insight into the correct orientation of the proximal and distal stumps with respect to each other. The surgeon should note this orientation and can place marking sutures in the epineurium on the superficial surface of the nerve prior to performing a neurolysis and mobilizing the nerve segments. Visual cues such as the alignment of large epineurial blood vessels commonly encountered on major peripheral nerves provide an additional tool to ensure fascicular alignment. While in theory a grouped fascicular repair could most accurately realign fascicles, it may not be a practical option for several reasons. In traumatic nerve injuries, the fascicular anatomy may be distorted to the extent that accurate identification is not possible. Additionally, a grouped fascicular repair necessitates increased intraneural dissection as well as the placement of intraneural sutures, both of which may lead to scarring within the nerve that could impair regeneration. Given these considerations, the vast majority of nerve surgeons perform an epineurial repair. Gently coapting the edges of the nerve together can allow space for mismatched fascicles to find their appropriate distal target with the help of neurotrophic and chemotactic factors, taking advantage of the intrinsic properties of neurotropism.

A tension-free nerve coaptation is critical for successful axon growth across the repair site. Tension creates two fundamental problems. First, a repair under significant tension is at risk of pulling apart and forming a critical gap across which sprouting axons cannot reliably regenerate.

Second, tension itself has physiologic effects on the repaired nerve. Above a certain threshold, strain on a nerve begins to decrease intraneural circulation. In a rabbit tibial nerve model, Lundborg and colleagues showed that between 8% and 15% strain there is a precipitous drop in intraneural circulation [74]. Below 8%, nerve elongation blood flow was not affected; however, at 8% strain, a detectable decrease in the flow of epineural and perineurial venules occurred, though intra-fascicular and capillary flow remained unaffected. Above 8% strain they observed a gradual and continuous decrease in arterial blood flow until blood intra-fascicular capillary and arteriole flow ceased at 15% strain. This strain-dependent decrease in intraneural blood flow is presumably a result of tension-induced increases in intra-fascicular pressures when the nerve is placed on stretch. Above the critical 15% strain level, nutrition to an already injured and regenerating nerve is impaired. Furthermore, tension on a nerve has been shown to negatively affect nerve conduction independently of nerve ischemia. Rabbit sciatic nerves placed at 16% strain for a 1 hour period showed an irreversible 30% drop in conduction velocity that was independent of recovery of blood flow following relaxation [29]. Similar effects on conduction velocity with stretched repairs were reported by Terzis et al., and tension-induced connective tissue proliferation may provide an obstructive barrier to axonal bridging across the coaptation site.

The resistance to stretch of a peripheral nerve will vary by the ratio of connective tissue to axons and the degree of elasticity of the connec-

tive tissue of the nerve. As mentioned above, anatomic regions where nerves are physiologically subjected to strain, such as across joints, display a higher percentage of connective tissue surrounding and within fascicles. Like other connective tissues, nerves exhibit time-dependent mechanical creep stress relaxation, which allows them to accommodate to a low level of tension placed on a repair [75]. A safe baseline would be to keep the degree of strain on both the proximal and distal nerve segments to less than 10% [76].

In clinical practice, surgeon judgment is used to make the determination of how much tension is too much tension for a primary nerve repair. A useful heuristic to help make this determination is the breaking or pullout strength of a single epineurial suture. Experimental data from a cadaveric study evaluating median nerve repair indicates that an epineurial repair with a single 9-0 nylon suture will reliably fail by suture breakage at a strain of between 5% and 8% [77]. The 8-0 nylon and prolene sutures tended to fail by pullout rather than breakage, and strain at failure exceeded 9% in some specimens. Thus, if a single 9-0 nylon is able to bring together the two ends of a nerve coaptation without the suture breaking, this indicates that the level of strain is likely below what would be deleterious to nerve regeneration. An epineurial repair is performed with as few 9-0 nylon sutures as necessary to align the two nerve ends and provide sufficient strength to resist gapping when the nerve is placed on gentle stretch. Many surgeons reinforce their suture repair with a fibrin glue sealant to decrease the chances of gapping.

Flexion of joints and positioning can at times aid to take tension off of the nerve coaptation. Postoperative splints can be used to gently flex joints that are then gradually extended in the postoperative period. However, it is of paramount importance to avoid reliance on joint positioning to the extent that a contracture is induced. The repair should be checked for gapping through a full range of motion of adjacent joints prior to wound closure to help guide the positioning of postoperative immobilization.

1.4.1.1 Nerve Grafting

When a tension-free primary nerve coaptation cannot be achieved, the nerve gap must be bridged by an interposition graft. The graft serves as a scaffold for sprouting axons to grow from the proximal to distal nerve stump en route to reinnervating their end target. Currently available options for bridging a nerve gap include autologous nerve graft, processed nerve allograft, and synthetic nerve conduits.

1.4.2 Autologous Nerve Grafting

Autologous nerve graft, or autograft, is still held by most peripheral nerve surgeons to be the "gold standard" for nerve grafting and the go-to choice for grafting of motor nerves and longer gaps in critical sensory nerves. The sural nerve is the most commonly used donor nerve given the length of available graft and well-tolerated resultant sensory deficit. The sural nerve can be used as a single nerve graft or several grafts together in parallel (a "cable graft") in order to provide a better size match for larger, poly-fascicular nerve repairs (Fig. 1.11). However, a number of additional donor options exist, including the anterior interosseous nerve (AIN), posterior interosseous nerve (PIN), lateral antebrachial cutaneous nerve (LABCN), medial antebrachial cutaneous nerve (MABCN), among others [78]. Each of these nerves has different cross-sectional areas and fascicular numbers, which can be taken into account to choose the optimal donor graft for a particular nerve reconstruction [79].

Some authors have reported the use of expendable motor nerves, such as the obturator nerve, for autograft reconstruction of motor and mixed peripheral nerves [80]. The authors cite an advantage of avoiding the sensory deficit in the donor distribution and the chance for neuroma formation or neuropathic pain at the donor site. The rationale for use of a motor nerve graft comes from animal research that has suggested that the internal architecture and neurotrophic factors unique to motor nerves may make them better suited to guide regeneration of a mixed periph-

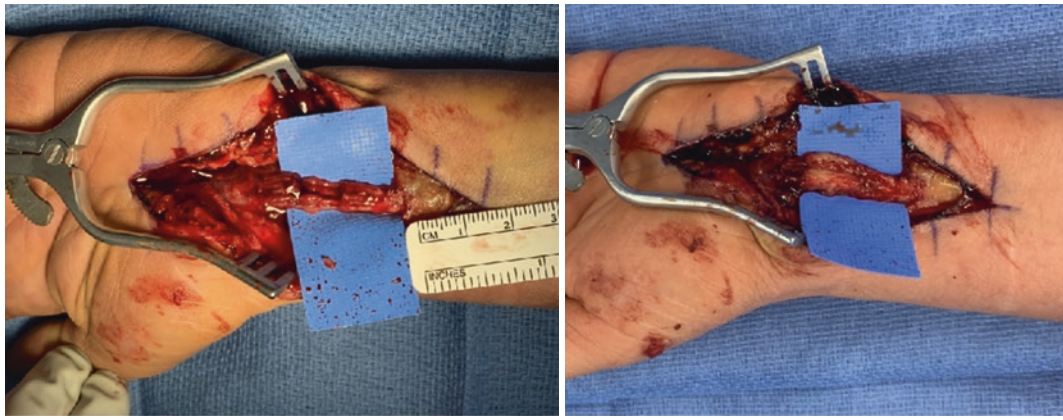

Fig. 1.11 Resection of neuroma in continuity from the median nerve (left) with subsequent sural nerve grouped fascicular repair using sural nerve autograft (right)

eral nerve defect due to so-called "modality-specific regeneration" [81]. Experiments by Mackinnon and colleagues have shown that the enhanced regeneration with use of a motor nerve graft is not seen with grafting of a pure motor nerve, only with grafting of a mixed sensory and motor nerve [82]. They hypothesize that the larger endoneurial tubes in a pure motor nerve may provide a better environment to permit directional sprouting when both motor and sensory axons are attempting to regenerate down the same graft. While these considerations merit further investigation, there is currently no clinical evidence to support the routine use of an autologous motor nerve donor for grafting of peripheral nerve defects.

Outcomes of nerve autografting have been reported in a number of retrospective case series and comparative studies, many of these in the upper extremity. However, interpretation of these results is challenging due to the heterogeneity of injury types and concomitant soft tissue damage, patient ages, delay to surgery, and technical details of repair – all of which have been shown to influence nerve regeneration. Sensory recovery following autologous nerve grafting is length dependent. For example, in a large series of over 100 digital nerve repairs with autograft, the vast majority of patients with gaps 2 cm or less demonstrated S3 or better sensation, while only two-thirds of patients with gaps 2–5 cm and very few with gaps >5 cm achieved this level of recovery [83]. A recent meta-analysis affirms excellent results for autograft repair of digital nerve gaps between 2 and 3 cm in length, with approximately 50% of patients achieving S4 recovery and 88% achieving S3+ or better. Over 50% of patients repaired with autograft achieved <6 mm static 2PD [84]. With respect to motor and mixed nerves, Ruijs et al. performed a meta-analysis of 23 studies and 623 median and ulnar nerve repairs using autograft and showed that 47% of patients recovered M4 strength and 40% of patients recovered at least a sensory recovery of pain and touch sensation without hyperalgesia (S3+) [85]. These numbers are useful as a rough estimate, though gap width and level of injury data were incomplete which precluded a more granular stratification of outcomes based on these variables.

Despite a proven track record, there are a number of disadvantages to nerve autografting. The main disadvantage is that an autograft results in donor site morbidity, has a finite length, and carries a risk of complications at a second surgical site, including increased operative time, wound healing problems, scar sensitivity, neuroma, or neuropathic pain. As a result, much effort over the past 30 years has been devoted to the development of alternatives to the use of autologous nerve grafts.

1.4.3 Nerve Conduits

A nerve conduit is a hollow tube that provides a relatively closed environment for axonal sprouting and regeneration from the proximal to distal segments of a cut nerve. The idea is that when the two ends of the nerve cannot be directly coapted, the conduit serves as a channel to permit the diffusion of neurotrophic growth factors and provide a mechanical barrier to the loss of axonal sprouts in order to increase the efficiency of regeneration. Extruded fluid trapped within the conduit forms a fibrin matrix that serves as a structural framework to guide axonal regeneration across the gap. The cross-sectional area of the fibrin bridge between nerve ends within a conduit decreases as the length of nerve gap is increased, limiting axonal bridging [86].

Modern conduits are fabricated from biocompatible, absorbable synthetic materials such as type I collagen, polyglycolic acid (PGA), and polylactide-caprolactone. Excellent results have been reported for the use of PGA conduits for short sensory nerve gaps, and it has compared favorably to both direct repair across a small gap and use of nerve autograft. A prospective, multicenter study comparing digital nerve repairs with PGA conduits to either direct repair or nerve autograft showed a higher proportion of excellent results and lower mean two-point discrimination for repairs utilizing the PGA conduit for both short nerve gaps and nerve gaps greater than 8 mm, ranging up to 25 mm [87]. Another large series on use of PGA conduits for sensory gaps less than 25 mm reported 94% meaningful recovery with an average static two-point discrimination of 8 mm [88]. In this study, patients were prospectively randomized to either PGA conduit or autologous vein conduit; no difference was found in sensory recovery, with the cost of the conduit offset by the cost of the additional surgical time need to harvest the vein. Similar outcomes have been reported with collagen conduits [89, 90]. While polycaprolactone has also shown some success in short sensory nerve gaps, high reported complications, including nerve irritation, extrusion, and fistulization with wound formation, have limited widespread adoption [91, 92].

Based on the accumulated body of evidence on the use of nerve conduits since their introduction in the 1980s, conduit use is limited to reconstruction of short sensory nerve gaps, <3 cm in length. Studies on the use of conduit for mixed and motor nerve defects yielded disappointing results, with the majority demonstrating minimal meaningful motor recovery, even for short nerve defects [93, 94]. A recent comprehensive review of conduit use confirmed that there is insufficient high-quality evidence to support the use of nerve conduits in larger gap motor or mixed motor/sensory nerves [95].

1.4.4 Processed Nerve Allograft

Processed nerve allograft is a commercially available product prepared from cadaveric nerves through a process of chemical decellularization to remove myelin and Schwann cells, leaving behind the endoneurial basement membrane architecture, extracellular matrix proteins and glycosaminoglycans, and neurotrophic factors to guide axonal regeneration. Revascularization of the allograft occurs via epineurial vessels at the proximal and distal coaptation sites [96]. Allograft has supported the regeneration of myelinated axons across gaps as long as 4–6 cm in animal models – longer regeneration is limited by the inability of Schwann cells to migrate further along a processed nerve allograft [97, 98]. Avance nerve graft by AxoGen is currently the only commercially available processed nerve allograft on the market and is available in diameters up to 5 mm and lengths of 10, 30, 50, or 70 mm.

Support for the use of allografts has been bolstered by the RANGER study (Registry Study of Avance Nerve Graft Evaluating Recovery Outcomes), an ongoing, multicenter, prospective longitudinal study to assess outcomes using processed nerve allograft for sensory, mixed sensory/motor, and pure motor peripheral nerve gaps. A number of studies from

the RANGER cohort have established efficacy of Avance nerve graft for short sensory nerve repairs, <3 cm. Cho et al. reported meaningful recovery for 89% of digital nerve repairs, as defined as S3 or S4 recovery, with a mean gap length of 2.3 cm and range up to 3.5 cm. Mean static two-point discrimination for these patients was 8 mm [99]. More recent follow-up data from this same cohort looking at larger digital nerve gaps, averaging 3.5 cm and ranging up to 5 cm, showed similar outcomes with the majority achieving S3+ recovery [100]. A meta-analysis of the literature to date on use of processed nerve allograft for digital nerve gaps less than 2.5 cm showed equivalent results to autograft for sensory recovery [84].

Safa et al. recently reported on outcomes of mixed and motor nerve reconstructions from the RANGER cohort with a mean follow-up of more than 2 years [101]. Outcomes included nerve-specific functional testing for British Medical Research Council grade, as well as pinch and grip strength. Twenty-two patients with a mean age of 38 years met inclusion criteria. Mean gap length was 33 mm, ranging from 10 to 70 mm, and all repairs were acute, averaging 9 days after injury. Overall, 73% of patients achieved meaningful motor recovery (defined as M3 or greater), while 50% of patients achieved a higher threshold of recovery (defined as M4 or greater). Outcomes were stratified by gap length, with findings of 80% meaningful motor recovery (defined as M3 or greater) for a gap of 10–25 mm, 62% for a gap of 26–49 mm, and 76% for a gap of 50–70 mm. Median nerve repairs performed better than ulnar nerve repairs, though the study was not powered for this comparison. This study was limited by a small sample size, though it does provide some support for the use of processed nerve allograft for mixed and motor nerve defects up to 7 cm in length. While these results are encouraging, data from the RANGER cohort to date is still not considered sufficient by most peripheral nerve surgeons to indicate the routine use of processed nerve allograft in lieu of autograft for critical motor and mixed nerve gaps when sufficient donor nerve is available [95].

1.4.5 Future Directions in Nerve Recovery and Repair

The use of immune modulation by administration of tacrolimus (FK506) has garnered attention in the literature as a technique for improving peripheral nerve regeneration, as it has shown some tendency to improve results of immediate nerve repair when given at the time of nerve transection in a rat model. The mechanism by which FK506 improves regeneration is unclear, but possible mechanisms include a generalized decrease in inflammation, faster restoration of the blood–nerve barrier, effects on calcium levels, and modification of signaling pathways [102]. FK506 treatment has been shown to result in a transient increase in ED2-positive macrophages compared to controls, but not ED1-positive macrophages [103]. Local administration of FK-506 has shown better functional results than systemic administration in a rat model [104] and better axonal regeneration when applied topically in low doses [105]. The effects of a delay in administration of FK-506 are less clear, with one study showing diminished effects on axonal regeneration, particularly when repair is also delayed [106].

Polyethylene glycol (PEG) fusion is another technique that has gained attention in recent years for its ability to rapidly restore nerve continuity and function. Mammalian nerves have the capability to perform plasmalemmal sealing after transection to help mitigate further damage. More recently, polyethylene glycol, in conjunction with methylene blue, has been utilized to promote fusion of the transected fascicles after close approximation with sutures [107]. The cut ends must be washed with calcium-free hypotonic saline and treated with an antioxidant (methylene blue), followed by polyethylene glycol [108]. This results in return of nerve action potential minutes after repair and more rapid recovery of function over the course of days to weeks [109–111]. Clinical implementation of this technique may be limited due to the need to perform membrane fusion prior to the release of the mitochondrial calcium, the critical event that destabilizes the axonal membrane and triggers Wallerian degeneration. While PEG fusion has been suc-

cessfully performed up to 24 hours after injury [112], it seems unlikely the window for intervention will extend beyond 1 day, due to the inevitable initiation of Wallerian degeneration. This will pose a formidable challenge in successful adaptation of this technique to clinical practice, but early findings give hope that future research may identify additional ways to prevent Wallerian degeneration and improve outcomes after nerve injury.

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