

Anatomy and Physiology of Peripheral Nerve Injury and Repair

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ABSTRACT

The management of peripheral nerve injury continues to be a major clinical challenge. Despite advancements in microsurgical technique, results after nerve repair have been unpredictable and disappointing. The management of these nerve injuries relies on having a thorough understanding of peripheral nerve anatomy. This is the basis of the classification schemes by Seddon and Sunderland, in which the prognosis of nerve injuries varies depending on the degree of injury to their substructures. The most recent advances in the management of peripheral nerve injuries rely on the ability to manipulate the pathophysiologic processes triggered by nerve injuries and regeneration. End-to-end primary repair should be sought whenever a tension-free repair can be attained. If there is a significant nerve gap, use of nerve autograft remains the gold standard. In nerve injuries where a nerve autograft is not possible, the use of nerve allograft, as well as autogenous, biodegradable, and synthetic nerve conduits has shown promising results in experimental studies.

The refinement of microsurgical technique in the past two decades has provided better results in peripheral nerve repair. Improved knowledge of the internal topography of the peripheral nerve has also contributed to better outcomes of peripheral neurotomy. Nevertheless, the management of peripheral nerve injuries remains a clinical challenge. Restoration of nerve function, especially sensory function, is usually not fully achieved. Improvements in microsurgical technique have reached a plateau. Researchers are now focusing on the manipulation of the pathophysiology of peripheral nerve injury and regeneration to improve clinical outcome. The objective of the present review is to discuss the relevant peripheral nerve anatomy and pathophysiology of nerve injury as it pertains

to recent advances in treatment. The classification schemes used as basis for treatment and determination of prognosis will also be discussed.

ANATOMY

To better understand the pathophysiologic processes in nerve injuries, it is essential to know the anatomy of a peripheral nerve and have a solid understanding of its various components and intraneural arrangements. The normal peripheral nerve is composed of connective tissue and nerve components. These connective tissue structures, the endoneurium, perineurium, and epineurium, all form the framework that organizes and protects the nerve fibers and axons (Figure 1).

The smallest functional units in the peripheral nerve are the nerve fibers. These nerve fibers can be either unmyelinated or myelinated. Unmyelinated nerve fibers are composed of several nerve axons, which are enveloped as a group by a single Schwann cell. Myelinated nerve fibers consist of a single axon that is enveloped individually by a single Schwann cell. The membrane of this Schwann cell wraps around the nerve fiber to form a multilaminated myelin sheath. The axon is enveloped along its course in the myelinated nerve fiber by multiple, end-to-end Schwann cells. The length of the axon covered by a single Schwann cell is called an internode. The short distance between

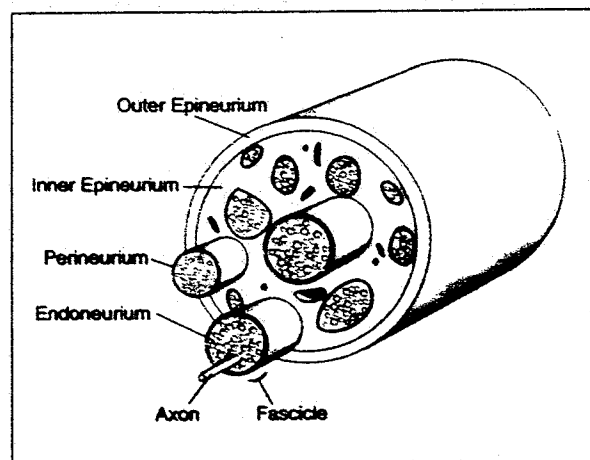


Figure 1. Schematic illustration of the cross-sectional anatomy of a normal peripheral nerve showing the connective tissue and nerve tissue components.

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Schwann cell processes, in which the axon is not myelinated, is known as the node of Ranvier. Local supporting connective tissue consisting of thin collagen fibers known as the endoneurium supports each myelinated nerve fiber or group of unmyelinated nerve fibers. Groups of endoneurium-sheathed fibers, called a fascicle, are surrounded by a thin, dense, multilayered connective tissue sheath known as the perineurium.

Important functions of the perineurium are to maintain the intrafascicular pressure and to regulate the local environment in the intrafascicular (or endoneurial) space by acting as a diffusion barrier to several substances. The perineurium may also serve to protect the nerve fibers from infectious agents, as illustrated by the fact that nerves can pass through pyogenic infections with preserved function. Connective tissue termed the interfascicular or inner epineurium then surrounds each individual fascicle. This tissue is surrounded by a sheath termed the outer or extrafascicular epineurium, which serves as the surrounding envelope of the peripheral nerve trunk.

The main function of the epineurium is to protect the fascicles and maintain the structural continuity of the nerve. The interfascicular epineurium facilitates motion between the individual fascicles. Fibrosis of such structures, as may be seen with chronic nerve compression, will inhibit longitudinal gliding. The epineurium generally makes up about 50% of the cross-sectional area of the nerve trunk. After surgical nerve repair or chronic nerve compression, the epineurium may thicken and adhere to the surrounding tissue. This, in turn, may prevent gliding of the nerve and cause tethering at the affected site, which may result in a superimposed traction injury. A layer of loose areolar tissue around the outside of the nerve is known as the mesoneurium. This tissue is continuous with the epineurium and extends to the surrounding tissue. It is critical in maintaining longitudinal excursion of the peripheral nerve. Although the existence of this structure has been questioned by some, its existence is supported by most.¹

The peripheral nerve is supplied by both an external segmental blood supply and an intrinsic longitudinal blood supply. Recent studies have shown the intrinsic blood supply to be extensive as it exists in the epineurium, perineurium, and endoneurium.^{2,3} Whereas large vessels can be found in the epineurium and endoneurium, only capillaries are found in the endoneurium. The segmental blood supply enters the nerve via the mesoneurium.

NERVE INJURIES

Nerve injuries can be produced by various mechanisms. These include crush trauma, direct laceration, stretching, and compression. The two most widely accepted classification schemes to characterize the injuries are Seddon and coworker's⁴ and Sunderland's⁵ classifications. In 1943, Seddon and colleagues⁴ described three types of nerve injury: neurapraxia, axonotmesis, and neurotmesis. Sunderland⁵ later expanded this classification into five different nerve injury patterns. This description is more detailed, as it classifies the type of injury according to the structures that are damaged. Neurapraxia and axonotmesis are classified as first- and second-degree Sunderland injuries, respectively. This classification has also added two types of intermediary nerve injuries, third and fourth degree, and has classified neurotmesis as a fifth-degree injury.

Neurapraxia, or first-degree Sunderland injury, is the mildest injury pattern that has been observed. Such injury involves a local conduction block at the site of injury along the course of the nerve, with normal conduction both proximal and distal to the site of injury. The nerve remains in continuity and no axonal injury is present. If there is any evidence of histopathologic change, there may be areas of segmental demyelination. The usual mechanism for this injury is compression, as seen in nerve entrapment syndromes, such as tourniquet palsy or other localized pressure palsy. Full functional recovery is to be expected within a few days to a few weeks.

In axonotmesis, or second-degree Sunderland injury, there is axonal disruption with subsequent Wallerian degeneration distal to the site of injury. There is an attempt at regeneration through axonal sprouting proximal to the site of injury. This type of injury is purely axonal in nature. The endoneurium and perineurium remain intact and therefore facilitate nerve regeneration, as regenerating axons follow their normal course and arrive at their original target. The Schwann cells enveloping the injured axons also remain intact, which allows regeneration to restore full motor and sensory function. Recovery in these injuries will occur at the classic rate of nerve regeneration of approximately 1 mm/day to 1.5 mm/day, or 1 inch/month.^{4,5} The rate of regeneration can be monitored with a present advancing Tinel sign as it progresses from proximal to distal.

The diagnosis of whether a nerve injury after a closed stretch injury is a neurapraxia or an axonotmetic type of injury can only be made after recovery of the nerve has been observed. If full recovery

occurs within the first 3 months of injury, then the injury is classified as a neurapraxia injury, or first-degree injury. If the recovery is full, but occurs at a rate of 1 inch/month and a Tinel sign is present, then the injury is classified as the axonotmetic injury, or second-degree type of injury.

Third-degree types of injuries, as expanded by Sunderland,⁵ include damage to the endoneurium. Therefore, axons must regenerate through some degree of scar tissue. This can lead to incomplete regeneration, as some of the regenerating fibers do not achieve contact with distal receptors or end organs because of interposed scarring within the endoneurium. The basal lamina of the Schwann cells is also damaged in this type of injury. This can lead to mismatching of regenerating nerve fibers to inappropriate distal receptors. The epineurium is not damaged in these injuries, and therefore the nerve fibers within the confines of epineurium will remain and regenerate within that fascicle. This is relevant as injuries that occur relatively proximal in the extremity where motor and sensory fibers are adjacent to each other within a fascicle may produce abnormal motor and sensory recovery. Recovery in this type of injury occurs at the same rate as axonotmesis, approximately 1 inch/month with an evident advancing Tinel sign. Unlike axonotmesis, however, the degree of recovery will not be complete. The recovery pattern can be quite varied and can range from almost complete recovery to very minimal recovery, depending on the degree of endoneurial scarring present and on the mixture of motor and sensory fibers in the fascicles involved.

Fourth-degree Sunderland injuries involve widespread damage to the myelin, endoneurium, and perineurium, along with axonal disruption. The epineurium remains intact, so that in gross appearance the nerve remains in continuity, but diffuse intraneural scarring blocks regrowing axons from reaching their destination. A Tinel sign will be present at the level of the injury, but no progression will be noted distal to the injury because of blocking of regenerating nerves by scar tissue. These injuries will never show any signs of motor or sensory recovery unless surgical reconstruction with nerve grafting or nerve conduits is undertaken. They are usually a result of very severe stretch or traction injuries, and a period of observation of approximately 3 months is recommended. After 3 months, first-, second-, and third-degree injuries will have become evident and will show signs of recovery. Injuries that do not show any evidence of recovery at this time are considered to be Sunderland fourth-degree injuries and should be

considered for surgical management.

Complete transection of the peripheral nerve is known as neurotmesis, or a fifth-degree Sunderland injury. This injury is the most severe type and is easier to diagnose initially as it is usually associated with an open traumatic injury. In recent years, a sixth-degree injury has been added to Sunderland's classification.⁶ This type of nerve injury combines all or many of Sunderland's five degrees of injury. It involves a mixed pattern of injury in a peripheral nerve in which some fascicles only sustain a first- or second-degree Sunderland injury, whereas others sustain a fourth- or fifth-degree injury. Therefore, patterns of recovery are mixed, with more complete recovery observed in the fascicles with lower degrees of injury. These injuries can be challenging to manage because the extent of nerve injuries can be difficult to classify even with electrodiagnostic tests. These tests can differentiate between first-degree Sunderland injuries (neurapraxias) and other type injuries (degrees II to VI). However, they cannot differentiate between lesions that will achieve eventual recovery (degrees I-III) and those that will not achieve eventual recovery (degrees IV and V). It is ultimately the responsibility of the surgeon to clinically determine the degree of function in the extremity to assess the degree of injury in the various fascicles along a peripheral nerve.

PATHOPHYSIOLOGY OF NERVE INJURY

After a peripheral nerve sustains a traumatic injury, complex pathophysiologic changes, including morphologic and metabolic changes, occur at the injury site. These complex changes also occur in the nerve cell body, in the segments proximal and distal to the injury site, and in the distal endings of both muscle end-plates and sensory receptors. It is essential to have a good understanding of the series of events involved in the repair process, as these become relevant in the timing and technique of nerve repair. Changes can be seen in the nerve cell body as early as several hours after the injury. The series of morphologic changes that ensue in the cell body after injury are known as chromatolysis, and entail cell body and nucleolar swelling, and nuclear eccentricity. The metabolic changes that are seen within the neuron involve an increase in the synthesis of RNA, protein components, and lipids, as well as an increase in glucose-6-phosphate dehydrogenase and hydrolytic enzyme production. All of these changes involve an alteration of the metabolic machinery from being primarily concerned with transmitting nerve impulses to fabricating structural components for reconstruction of the injured nerve.^{7,8}

These changes occur in both the dorsal root ganglia in sensory neurons and in the anterior horn of the spinal cord in motor neurons.

Changes in the nerve at the site of injury begin almost immediately. Within hours after injury, the axons will sprout into multiple regenerating axons.^{9,10} Recent research shows that Schwann cells play an important role in nerve regeneration at the site of injury. Schwann cells elaborate processes that serve as physical conduits that guide axons to their targets. The rate of axon regeneration is limited by the extension of these Schwann cell processes rather than by axonal growth.¹¹ The regenerating units will initially lack myelin even when the parent axon is a myelinated fiber. With time, these unmyelinated fibers will become myelinated.

After nerve transection, the distal segment undergoes a slow process of degeneration known as Wallerian degeneration. This process starts immediately after injury and involves myelin breakdown and proliferation of Schwann cells. Schwann cells and macrophages are recruited to the injury site, and over a period of 3 to 6 weeks, they phagocytize all the myelin and cellular debris, and ultimately leave endoneurial tubes, which essentially consist of the basement membrane of these Schwann cells. These proliferating Schwann cells organize themselves into columns, and the regenerating axons associate with them by growing distally in between their basal membranes.

Changes in the levels of neurotrophins within both the proximal and distal stump also occur. Neurotrophin 4/5 mRNA in the distal stump is increased, as well as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). NGF is known to be secreted by Schwann cells after axotomy.^{12,13} In sensory nerves, neuropeptides such as substance P decrease, whereas vasoactive intestinal peptide (VIP) and cholecystokinin increase.¹⁴

Changes in the surrounding cells include marked proliferation of Schwann cells, perineurial cells, and epineurial cells. Laminin, neuronal cell adhesion molecule, L1, and tenascin are all increased on the surface of Schwann cells and/or the surrounding extracellular matrix after nerve injury.¹⁵ During Wallerian degeneration, Schwann cells proliferate and macrophages invade the distal stump. Most of the myelin debris and axonal debris is phagocytosed by the macrophages.

Changes in the muscle and sensory organs are also important. The changes in the muscle include shrinkage of the cells, thickening of the perimysium and epimysium, and atrophy of the spindle cells. Complete muscle cell atrophy is seen at 2 to 6 weeks. Fibrosis between motor fibers develops 12 to

24 months after injury, and fragmentation and disintegration of a denervated muscle can be established at 2 years after the nerve injury. These changes limit functional motor reinnervation. Unlike the motor system, recovery of protective sensibility is possible years after nerve injury. Although a critical time period has not been determined, it has been suggested that functional sensation (two-point discrimination) decreases with a delay in repair longer than 6 months.¹

NERVE REPAIR

Nerve repair has undergone advances in the last 20 years. Controversy exists regarding technique and timing of neurography. The surgeon faced with repairing a nerve has multiple alternatives. Numerous attempts were made in the 1800s and the early 1900s to successfully repair nerves. Letievent¹⁶ in 1872 used a double-flap repair technique. Markoe¹⁷ in 1885 attempted a tangential repair process. Rawa,¹⁸ also in 1885, attempted a side-to-side repair. However, these early attempts were all unsuccessful.

Primary anastomosis is the procedure of choice whenever tension at the repair site can be minimized. Current techniques to repair nerves include two basic types of repair, epineurial repair and fascicular repair. Epineurial repair involves suturing of the epineurial sheath. The alignment of the fascicles is based on lining up anatomic landmarks on the surface of the nerve for repair (Figure 2). Fascicular repair includes sutures in the perineurium to reconstruct the continuity of the individual fascicles or groups of fascicles (Figure 3). Although there have been multiple clinical and experimental studies comparing the two techniques, these have yielded mixed results.¹⁹⁻²² The only prospective comparison of both techniques has shown no difference in results.²³ Whereas theoretically fascicular repair would seem to be a better method, there is no clinical evidence showing it to be superior. This may be because of the potential of mismatch of the fascicles during repair and the increased intraneural scarring that accompanies the increased manipulation of the nerve. Another reason that fascicular repairs have not been shown to be superior is the potential for fascicular repairs to result in mismatched repair of specific fascicles and therefore to result in decreased function of the repaired nerve. Epineurial repair, although less exact, may allow neurotrophic effects to aid in appropriate matching of proximal and distal fascicle ends. When misalignment occurs with epineurial repair, neurotrophic effects may play a role in directing nerve regrowth.

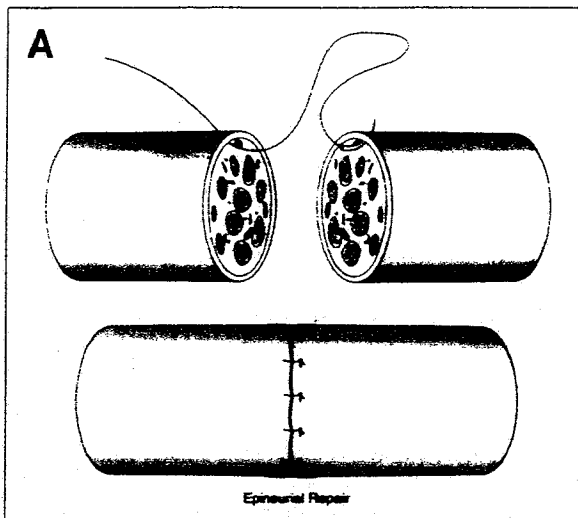


Figure 2. Schematic illustration of epineurial repair technique.

It is technically difficult to realign severed nerves because of branching of individual fascicles. Fascicular patterns can be highly variable in large mixed nerves within a relatively short distance. Techniques used for realignment include matching of fascicular groups according to size and shape, alignment of longitudinal blood vessels in the epineurium, electrodiagnostic methods, and histochemical staining.⁶

Nerve grafting is a technique that allows the repair of a nerve gap that cannot be reconstructed by direct end-to-end suture. This may be the case in injuries where trauma has caused segmental loss of a peripheral nerve, delay in primary repair has caused retraction of the nerve stumps, or segmental resection of a nerve has been necessary for treatment of a primary or surrounding malignancy. Nerve grafting should be performed whenever a tension-free repair cannot be attained. If tension can be minimized, primary anastomosis is preferred, because regeneration through grafts may be less successful in the presence of intrinsic mechanical differences, such as nerve diameter and fiber sizes. Furthermore, graft material is a poor provider of tropic and trophic factors necessary for nerve healing. Although small defects can be treated with mobilization of the nerve both proximally and distally, this should be avoided when any adjacent joint motion may result in tension across the anastomosis. Tension at the repair site compromises the blood flow in the repaired nerve. Studies have shown that just an 8% elongation of the nerve results in a transient 46% decrease in perfusion.²⁴ Increased tension also promotes scar formation and adhesions at the repair site. The gold standard in nerve gap management remains autogenous

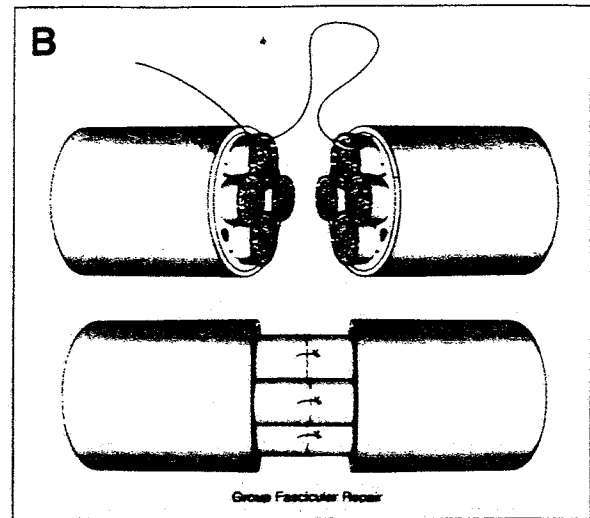


Figure 3. Schematic illustration of group fascicular repair technique.

nerve grafting.²⁵ The most frequent donor nerves are the sural, lateral antebrachial cutaneous, and the anterior branch of the medial antebrachial cutaneous nerve.

Autogenous graft may not be sufficient to repair large segmental defects or multiply injured nerves. There has been historic interest in the use of nerve xenografts to manage large nerve gaps. However, the poor and unpredictable results in both experimental and clinical studies have resulted in little interest in pursuing xenograft transplantation.^{26,27} Recent work has been done with allograft donor nerves. At the present time, clinical application of peripheral nerve allografting remains under experimental investigation. Efforts to lessen graft rejection have recently focused on both decreasing the antigenicity of the graft and decreasing the immune response of the recipient. In a primate model, nerve regeneration across an allograft nerve has been shown to be similar to an autograft when the host is immunosuppressed with cyclosporin A or given placebo.²⁸ Allograft nerves have also been used successfully in humans. Sensory reinnervation of the sciatic nerve has been shown after repair of defect greater than 20 cm with multiple cable allografts.^{29,30}

It is well known that the results of autologous nerve grafts are not entirely satisfactory, because the procedure requires the sacrifice of donor nerves along with additional operative time. Therefore, another area under investigation is the use of conduits as nerve graft substitutes. A technique known as entubulation repair consists of suturing nerve stumps into a tubular guide to bridge the nerve gap. This allows the proximal portion of the nerve to be realigned to the distal seg-

ment, which entraps neurotrophic factors in the tube and decreases peripheral sprouting. Peripheral nerve regeneration has been attempted in animal studies with natural occurring substances such as artery, vein, collagen, mesothelium, muscle, and even omentum.⁵¹ A wide assortment of bioabsorbable and nonresorbable substances have also been investigated. Animal studies have shown significant regeneration within venous conduits,^{32,33} and clinical use in sensory nerve defects of up to 3 cm has shown results similar to nerve grafts.³⁴ Synthetic nerve conduits, such as silicone³⁵ and glycolide trimethylene carbonate (Maxon),³⁶ have also been used in animal studies. Regeneration across a 10-mm nerve gap has been shown in rats by using silicone tube repair.³⁵ Synthetic conduits have also been used in conjunction with small segments of interposed nerve graft to bridge a nerve gap. These "stepping stone" nerve grafts theoretically provide nourishment to growing axons and Schwann cells. These grafts have shown regeneration similar to single long conduits, but inferior to single long nerve grafts.³⁷ Despite their initial experimental success, synthetic conduits have been shown to cause chronic irritation, inflammation, and nerve compression.³⁸ Biodegradable conduits, such as polyglycolic acid (PGA) tubing, have also been investigated.^{39,40} Research in animal models shows good nerve regeneration across gaps spanned by PGA tubes.⁴⁰ Biodegradable collagen-based conduits have also been used in rodents and nonhuman primates. The use of a collagen nerve guide in nonhuman primates has shown similar recovery across 5-mm gaps to that obtained by direct suture repair of the median nerve.⁴¹ Animal studies that use muscle grafts as conduits have also been conducted.⁴²⁻⁴⁴ Nerve regeneration across these grafts has been favorable in rats.⁴³

Isolated clinical reports have described the use of nerve guides fashioned from PGA³⁷ or silicone tubes^{38,45} to repair human peripheral nerve. However, complications have been reported with such materials, such as extrusion from the repair site, kinking of a semirigid tube, neuroma formation, and persistent pain because of entrapment neuropathies.³⁸

There is a developing interest in alternative techniques by using synthesis and release of neurotrophic factors to aid in nerve repair.^{46,47} The use of neurotrophic factors, such as NGF,^{48,49} brain derived growth factor,⁵⁰ and ciliary neurotrophic factor,^{49,51} are currently under investigation. The addition of NGF to a local permeable reservoir has been shown to increase the quality of nerve repair.⁵² Nontrophic substances like collagen and laminin have also been used to enhance nerve growth.⁵³

SUMMARY

It is important for the surgeons who deal with peripheral nerve injuries to understand the anatomy and pathophysiology of peripheral nerve injuries. This becomes quite relevant during decision-making process in microsurgical technique repair. Important advances in the field of microsurgical technique in the past two decades have dramatically improved the management of peripheral nerve injuries. Despite these advances, clinical results are not optimal. Researchers have therefore shifted their attention to manipulation of the local physiologic processes during nerve regeneration. The search for the optimal alternative to autogenous nerve graft for significant nerve defects continues to evolve. Future research into nerve repair and regeneration will most likely focus on the neurohormonal control of nerve regeneration processes, which we are only beginning to understand.

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This paper will be judged for the Resident Writer's Award.