Pathophysiology of nerve injury

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Anatomy

Connective tissue

A normal myelinated nerve is represented in Fig. 1, which demonstrates the extensive connective tissue that makes up the major component of the nerve and provides the scaffolding for the axons and their Schwann cells. Early studies of peripheral nerve anatomy delineated much of the fundamental architecture. Key and Retzius [1] detailed the subdivision of epineurium, perineurium, and endoneurium. The loose areolar tissue external to the epineurium is termed the mesoneurium. It is continuous with the epineurium and is critical to the longitudinal excursion of peripheral nerves. Millesi [2] stressed the importance of the mesoneurium in aiding the movement of the nerve in its surrounding tissue bed. Millesi [3] has shown that the median nerve moves up to 9.6 mm with wrist flexion and slightly less with extension. Wilgis and Murphy [4] demonstrated that the median and ulnar nerves glide longitudinally approximately 7.3 mm and 9.8 mm, respectively, with elbow flexion. Nerve excursion is critical in normal physical activity, and chronic nerve compression or associated fibrosis may significantly impair the ability of a nerve to glide, resulting in pain or discomfort.

The outer sheath of the nerve is the external epineurium and is composed primarily of collagen and elastic fibers. The internal epineurium is the structure that invests the fascicles, which are composed of myelinated and unmyelinated nerve fibers [5]. Fascicles vary in quantity and in size; much of the variety depends on the anatomic level and position of the peripheral nerve. Fascicular anatomy of a peripheral nerve can consist of a single fascicle (monofascicular), few fascicles (oligofascicular), or many fascicles (polyfascicular) (Fig. 2).

Each fascicle is encircled by the connective tissue known as perineurium. The cellular make-up of the perineurium consists of collagen fibrils dispersed among perineural cells [6]. The perineural layer is a major site for selective permeability because of the tight junctions that form between adjacent perineural cells. Surrounding each individual axon is a loose gelatinous collagen matrix called the endoneurium [7]. Although the endoneurial tissue has some tensile strength, the perineurium provides the peripheral nerve with most of its tensile strength and elasticity [8].

The volume and quality of intra- and extraneural connective tissue varies among different nerves and within the same nerve at different levels and anatomic sites [5]. For instance, superficial nerves have been shown to have substantial increases in connective tissue as they cross joint surfaces. The sciatic nerve has been shown to consist of approximately 87% connective tissue as it crosses the hip, which may be the result of a local reaction to repetitive strain or as a protective mechanism of nature [5].

Neural topography

In the more proximal aspects of the extremities, there is a significant plexus formation between the fascicles, but the sensory and motor topography is
specific. In the distal aspects of the extremity, the plexus formation between fascicles is far less extensive. Sunderland [9] reported that the internal topography of peripheral nerves became increasingly more organized as they progressed distally (Fig. 3). Jabaley [10] has shown that nerve fascicles have significantly fewer interfascicular connections, or plexus formation, distally as compared with proximally in the extremity.

Jabaley [10] demonstrated that the recurrent motor branch of the median nerve can be readily dissected without plexus formation for approximately 70 mm, and the anterior interosseous nerve at the level of the medial humeral epicondyle can be separated proximally approximately 60 mm. The development of more functionally distinct fascicles in distal peripheral nerves allows a more extensive surgical dissection via internal neurolysis and provides a variety of reconstructive options (Fig. 4). Therefore, an understanding of the anatomical patterns and topography of different peripheral nerves is an essential component to peripheral nerve surgery [11].

**Blood supply**

The blood supply to peripheral nerves occurs via an intrinsic and extrinsic system. The intrinsic system circulates within the epineural sheath, and the extrinsic circulation is derived from small vessels outside of the nerve. These vessels can enter the nerve via one of three patterns: segmental with no dominant pedicle, one dominant pedicle coursing longitudinally with the nerve, and multiple dominant pedicles along the length of the nerve [12] (Fig. 5).

The external vessels enter the mesoneurium and communicate with the epineural space via the vasa nervorum. At this junction, a plexus formation develops and runs longitudinally within the perineurial
space. This plexus enters the endoneurium at an oblique angle to anastomose with the intrinsic circulation that surrounds each nerve fascicle. This junction is a site of potential circulatory compromise with increase in endoneurial pressure.

Many studies have shown that peripheral nerves have a well-developed intrinsic blood supply [13–15]. Breidenbach [12] used radioactive microspheres in the rabbit sciatic nerve model to evaluate intraneural blood flow. He demonstrated that a peripheral nerve could be raised independent of its extrinsic inflow without evidence of ischemic damage. He demonstrated that a nerve receiving flow from only one extrinsic blood vessel maintains perfusion over a diameter/length ratio of 1:45 without evidence of ischemic changes. This knowledge is useful when a peripheral nerve needs to be extensively mobilized (e.g., submuscular transposition of the ulnar nerve) and supports the theory of a robust and hardy intrinsic vascular system.

**Blood-nerve barrier**

A barrier system exists in the peripheral nerve that is an extension of the blood-brain barrier. The blood-nerve barrier is composed of the internal layers of the perineurial sheath and the tight junction of the endothelial cells of the endoneurial microvessels. These tight junctions regulate the intraneural environment and provide a level of immunologic protection. Smith et al [16] showed that the blood-nerve barrier is not functional before 13 days of life because clefts are present between the endothelial cells. After 16 days, these clefts are replaced by tight junctions, resulting in a blood-nerve barrier.

Nerve injury can result in a breakdown in the blood-nerve barrier at the level of the microvessels, resulting in an increase in pressure within the fascicle. The lack of a lymphatic circulation within the endoneurial space and subsequent unresolved edema within the compartment can interfere with the microcirculation of the fascicles [17]. Leaking capillaries within the endoneurium permits the eventual accumulation of fluid and proteins. As the pressure rises within the endoneurial space, a “mini compartment” syndrome can develop, resulting in ischemic damage to that portion of the nerve.

**Nerve fibers**

The basic neural structure is made up of axons and their accompanying Schwann cells. Nerve fibers are myelinated or unmyelinated. Sensory and motor nerves contain both types of fibers in a ratio of 4 unmyelinated to 1 myelinated. Unmyelinated fibers constitute 75% of cutaneous nerves and 50% of motor nerves. They are composed of several axons encircled by a single Schwann cell. In most cases, unmyelinated axons are small, with diameters averaging 0.15 to 2.0 μm. The axons of myelinated nerve fibers are individually enveloped by a single Schwann cell (Fig. 6). Histologically, the myelinated fiber consists of a center core of cytoplasm (axoplasm) surrounded
by a confluent membrane (axolemma) that is further surrounded by the Schwann cells laminar myelin sheath. The Schwann cells act as specialized satellite cells that can be identified definitively at the electronmicroscopic level by their double basement membrane [18,19].

At the junction between adjacent Schwann cells, the axolemma becomes exposed at a gap known as the node of Ranvier. This gap is where sodium channels cluster and are found regularly along the axon. The nodes of Ranvier aide in the propagation of the depolarizing action potentials along the length of

Fig. 4. (A) A cadaver dissection demonstrating the internal fascicles of the median nerve with the hand to the right of the page. (B) A closer view of the intraneural topography at the proximal arm above the elbow showing marked plexus formation between fascicles. (C) A closer view of the intraneural topography just distal to the elbow with less plexus formation. (D) A closer view of the intraneural topography at the wrist where little to no plexus formation exists. (From Mackinnon SE, Dellon AL. Surgery of the peripheral nerve. New York: Thieme, 1988. p. 7–8; with permission.)
the nerve. The myelinated portions of the axon act as insulated areas that accelerate axonal conduction as the depolarization wave “jumps” from node to node. This is referred to as saltatory conduction, and it increases the speed of transmission more than would be accomplished by simply increasing axonal diameter. Unmyelinated fibers are able to propagate electrical impulses at speeds of 2 to 2.5 m/s. Myelinated fibers, by contrast, propagate impulses at speeds ranging from 3 to 150 m/s [20,21].

Axons originate from their corresponding cell bodies, which are located in the spinal cord, dorsal root ganglion, and autonomic ganglia. Sensory nerve fibers originate from the cell bodies in the dorsal root ganglia and join other spinal nerves to connect with sensory end organs. Motor nerve fibers (along with presynaptic sympathetic ganglia) arise from the anterior horn of the spinal cord and terminate at the neuromuscular junction in the muscle. The presynaptic sympathetic ganglia send their axons out to the postsynaptic sympathetic ganglia in the periphery, which then go on to innervate blood vessels, skin, and hair follicles.

The majority of a neuron’s cytoplasm is included in the volume of the axon [22]. Ducker’s [22,23] analogy is pertinent: “If the central cell body were the height of an average man, it’s axon would be one or two inches in width and would extend more than two miles.” The diameter of nerve fibers correlates with the velocity of transmission and function. Nerve fibers have been classified by variation in diameter and speed. Group A fibers are the largest and fastest conducting fibers. They are mostly myelinated and take pulses in efferent and afferent directions. Group B fibers contain myelinated autonomic and preganglionic efferent fibers. Group C fibers are the smallest and slowest. They are usually nonmyelinated and serve in the transmission of thermoreceptive and interoceptive signals.

**Axoplasmic transport**

Axoplasmic transport can be divided bidirectionally into an antegrade and retrograde system. The transport process occurs via fast or slow transport in the antegrade direction and via a fast system in the retrograde direction. Axoplasmic transport maintains
the structure of the nerve and provides the functional capacity of neurotransmitters. Axonal transport is energy dependent and can be disturbed by systemic derangements and direct nerve injury. In 1941, it was noted that the poliovirus infections used retrograde axonal transport to reach the anterior motor horn [24]. Subsequent work by Droz and Leblond [25], using labeled amino acids, determined that the antegrade transport of neurotransmitter vesicles along the nerve occurred at a rate of 1 and 1.5 mm per day.

Slow antegrade flow (1 to 6 mm per day) is used for the transport of major neural building blocks such as actin, tubulin, and other components of microtubules and microfilaments. Materials synthesized at the cell body that have a functional role at the terminal axon, such as neurotransmitters, are moved

Fig. 6. Transverse section (uranyl acetate and lead citrate, ×13,000) demonstrating a Schwann cell nucleus with an associated double basement membrane.

Fig. 7. An electron microscopy (uranyl acetate and lead citrate, ×9895) of a peripheral nerve after injury demonstrating the process of regeneration and degeneration occurring simultaneously in the distal stump. (Right) A classic regenerating unit containing myelinated and unmyelinated fibers surrounded by perineurium. (Left) The unit demonstrates evidence of Wallerian degeneration with myelin debris. (From Mackinnon SE, Dellon AL. Surgery of the peripheral nerve. New York: Thieme, 1988. p. 18; with permission.)
at a rapid antegrade rate of up to 410 mm/d. Retrograde transport remains constant at 240 mm/d. It allows the return of spent neurotransmitter vesicles and neurotrophic factors for recycling [21,26–29].

Basic response to nerve injury

In 1850, Waller [30] described changes in the distal segment of the hypoglossal nerve of the frog after transection; these changes later became known as Wallerian degeneration. His microscopic examination of the changes that occur to the cell body and axon after nerve transection demonstrated evidence of distal degeneration. He also described the generation of neural tissue from the end of the proximal stump, which was later referred to as the “outgrowth” theory. Further investigation by Ramon y Cajal [31] established that nerve regeneration emanated as an outgrowth from the proximal stump of the severed axon (Fig. 7).

The transection of a peripheral nerve initiates a cascade of events (Fig. 8). The changes occur in the cell body, at the site of injury, and in the proximal and distal segments of the axon. After a central axotomy, the cell nucleus migrates toward the periphery of the cell body, and neuronal chromatolysis occurs. An increase in cellular volume occurs as the cell increases the production of RNA and associated regenerative enzymes. The cellular RNA production and overall metabolism increases at 4 days after injury, with a peak at 20 days [23,32].

The severity of injury and its proximity to the cell body influence the degree of neural cell death. The more proximal the injury is to the cell body, the more neuronal cell damage occurs. Ygge et al [33] studied the transection of the rat sciatic nerve and found a
27% neuronal loss after a proximal injury versus a 7% loss after a distal nerve injury. Similarly, they found that the more severe the injury, the more proximal the extent of injury.

Neuronal survival after axonal injury is age related. It is generally appreciated that younger children have superior functional recovery than adults. In a 15-year clinical study, Barrios and de Pablos [34] found that children recovered better than adults after peripheral nerve injury. However, there is evidence that a susceptibility to neuronal apoptosis exists in the neonatal period [35]. In a sciatic nerve transection model, when comparing a 6- versus 22-day-old animals, significantly greater motoneuron death was found in the younger group. It has been shown that the retrograde release of trophic factors from the target tissue is important for the survival of embryonic motoneurons [36]. Motoneurons early in the neonatal period are particularly dependent on growth factors [35]. Administration of nerve growth factor, ciliary neurotrophic factor, and neurotrophin-4/5 rescued a significant number (up to 30%) of motoneurons after sciatic nerve axotomy in 2- to 5-day-old mice. The administration of insulin-like growth factor, brain-derived neurotrophic factor, and neurotrophin-3 rescued the majority of axotomized motoneurons [37].

After injury, Schwann cells proliferate and migrate as Schwann cell columns (“bands of Bungner’’). The Schwann cell alters its phenotype and becomes non-myelinating, with stimulation transforming from a quiescent state to one of high mitotic activity and growth factor production [38]. Basement membrane components and cellular adhesion molecule production increases. This activity of the Schwann cells enables peripheral growth cone elongation. When Schwann cell migration is blocked by cytotoxins, regeneration does not occur [39,40].

**Site of injury**

Within 24 hours at the site of a peripheral nerve injury, a single axon produces multiple axonal sprouts, forming a regenerating unit [41] (Fig. 9). At the tip of these sprouts is a growth cone that has an affinity for the fibronectin and laminin of the Schwann cell basal lamina. Via contact guidance, filopodia in the growth cone explore the distal environment for the appropriate physical substrate [42–44]. The regeneration proceeds along the neural tube to reconstitute the axon at a rate between 1 to 4 mm per day. Without successful elongation, a neuroma forms. With successful reinnervation of the end organ, the number of axonal sprouts is modulated over a period of months to years [45].

Distal to the axotomy site, the nerve segment undergoes Wallerian degeneration. After transection, Schwann cell proliferation and myelin breakdown plays a prominent role. The Schwann cells and macrophages dispose of the axonal debris that forms with degeneration. Although the endoneurium and basement membrane remain essentially intact, the neural tube that forms eventually collapses as the myelin and axonal contents are digested. The process continues until the axons’ neural contents are fully resorbed, at which point the neural tube becomes replaced by Schwann cells and macrophages. The proliferative cells then organize into columns and form the “bands of Bungner’’ [46].

Although histologically similar to the Wallerian degeneration, axonal degeneration is more limited in the proximal segment. Depending on the severity of injury, the impact is often limited to one or a few of the nodes of Ranvier along the proximal segment [47,48]. The changes that occur in the proximal segment are referred to as “traumatic degeneration.”

In a sufficiently severe injury, in terms of energy and proximity, the degeneration can result in death of the cell body.

**Contact guidance and neurotropism**

In 1905, Ramon y Cajal [31] popularized the notion of chemical agents “attracting” nerve sprouts from the proximal stump of a peripheral nerve after injury. This concept was refined and became known as neurotropism, or directional guidance, by chemo-tactic factors. In 1944, Weiss and Taylor [49] demonstrated that neurregeneration across short nerve gaps did not seem to be related to an attraction by the distal stump, the proximal stump, or any other neurotropic effect. They proposed a mechanism of regeneration based on contact guidance. In a series of Y-shaped artery experiments, they showed that “…in no cases were the regenerating nerves attracted towards the peripheral nerve fragment but the fiber stream divided itself more or less evenly regardless of the kind of destination awaiting them” [49]. However, these results were influenced by an immunologic reaction to the aortic allografts (Fig. 10).

Additional work in the ensuing decades has expanded our understanding of the directional guidance of the regenerating axons. It is believed that that a motor axon sprouts into a regenerating unit that contains many axons. After axotomy, the pioneer motor axons initially regenerate along motor or sensory Schwann cell tubes. Upon the recognition of a motor cell tube, the leading motor axon signals back to the cell body. This results in further communication
Fig. 9. Light microscopy (Toluidine blue, ×655) demonstrating a nerve at different levels of a peripheral nerve injury. (A) Well-myelinated fibers in the proximal aspect. (B) Distal to the nerve injury, Wallerian degeneration is noted with areas of myelin debris. (C) Each nerve fiber will eventually sprout into a regeneration unit.
to the other motor axons within the regenerating unit to preferentially regenerate within that specific motor Schwann cell tube. Once the motor axons arrive at the distal muscle target, the motor axons mature, and those that regenerate toward sensory targets do not preferentially mature. However, motor axons that regenerate into inappropriate Schwann cell tubes are not specifically “pruned” away, as was previously thought. This phenomenon is known as “preferential motor regeneration” [40,50] (Fig. 11).

Fig. 11. Schematic diagram representing the concept of preferential motor regeneration after an axonotomy down a sensory or motor Schwann cell tube. (A) After the nerve is transected, the nerve fibers sprout into regenerating units. (B) The motor axons that regenerate into inappropriate sensory cell tubes do not preferentially mature. (C) The motor axons, however, are not specifically pruned away.
matrix than through a randomly oriented fibrin matrix or in a matrix free chamber. This further supported the role of the extracellular environment as a scaffold for the advancing regenerating nerve units.

The term “neurotropism” implies an ability to stimulate nerve maturation. Neurotrophins that participate in neural regeneration include nerve growth factor (NGF), brain-derived neurotrophic factor, neurotrophin 3, neurotropin-4/5, epidermal growth factor, insulin-like growth factor I and II, and glial-derived neurotrophic factor [51,53]. These factors are primarily produced by Schwann cells, which are known to become activated in the response to neural injury. Neurotrophins bind to specialized high-affinity tyrosine kinase receptors and to p75, a low-affinity NGF receptor [53]. Their role in neural regeneration is by indirectly acting on the Schwann cells by stimulating migration and adhesion to axonal projections. Through this mechanism, they play a key role in the progression of the axonal growth cone. Despite all these intricate mechanisms that are initiated, retrograde labeling indicates that up to 51% of the nerve fibers form inappropriate connections after significant nerve injury [54].

Nerve repair (end-to-side)

End-to-side neurorrhaphy, or latero-terminal neurorrhaphy, is the method of nerve repair whereby the distal end of a severed nerve is attached to the side of an uninjured nerve. In 1903, Balance [55] reported the first use of the end-to-side neurorrhaphy for the treatment of a facial palsy by the suturing of the distal end of the facial nerve laterally into the spinal accessory nerve. This concept was reintroduced in 1991 by Viterbo et al in animal and human studies [56]. Viterbo et al demonstrated in a rat study evidence of axonal ingrowth and the conduction of electrical impulses from a healthy nerve into the distal segment of a severed nerve after an end-to-side repair. Histologic evaluation distal to the repair site showed functional axonal regrowth and muscular reinnervation.

Our understanding of the regeneration process after an end-to-side neurorrhaphy is evolving. Uninjured sensory axons sprout de novo; however, whether or not motor axons have the same ability without an initiating local injury is debated [57]. Tarasidis et al [58] demonstrated an inferior recovery of motor nerve function when comparing end-to-side versus the end-to-end technique between posterior tibial and peroneal nerves in the rat at 16 weeks. Retrograde labeling showed that the vast majority of fibers regenerating from the proximal segment of the nerve were sensory. Noah et al [59] recommended the severance of the perineurium, or an “epineurial window,” for improved axonal regeneration when performing an end-to-side repair. They found the highest axonal counts when a perineurial window or partial neurectomy was performed [59]. Dvali and Hunter have recently demonstrated that motor axons sprout across an end-to-side repair if the donor nerve is crushed above the repair site, which suggests a different mechanism for sensory versus motor sprouting (unpublished observation).

Distal receptors

Once denervated, the muscle fibers undergo a process of atrophy. In 1944, Bowden and Guttmann [60] performed 140 muscle biopsies on Seddons patients and identified progressive atrophy and fibrosis in the first 3 years after denervation. Mammalian striated muscle after denervation has been shown lose 80% to 90% of its cross-sectional area with no loss of fiber numbers [5,61]. Additional studies indicated this process begins within 1 week of denervation [62]. In cross-sectional analysis, the normally eccentric nucleus of the muscle cell migrates centrally, creating the “target cells” found in denervated muscle [63,64]. Within 3 months of denervation, particularly if this is accompanied by lack of activity or movement, interstitial fibrosis replaces the muscle. By 2 to 3 years, the muscle seems to be essentially replaced by scar tissue or fat [63].

Reinnervation at the neuromuscular junction is dependent on the timely arrival of axonal regeneration in the region of the neuromuscular junction. The absolute time of denervation in which reinnervation is not possible is not known, but it is likely to occur after a 12-month period. Experimental evidence shows that an extended period from injury to repair further worsens the degree of ultimate recovery [65]. Age also plays a profound role in the ability for muscles to recover after denervation. Age-related decreases in muscle mass, force, power, and endurance are in part due to selective denervation of fast-twitch fibers. The reinnervation of denervated muscle fibers in old animals is not as successful as that seen in young animals [66–68].

Sensory organs

The end organ for sensory fibers consists of one of variety of specialized structures: Pacinian or Meissner’s corpuscles, Merkel cells, or free nerve endings (Fig. 12). Pacinian corpuscles receive a single axon terminal and are less likely to be reinnervated [69,70]. Alternatively, other mechanoreceptors, such as the...
Meissner’s corpuscles, Merkel cells, or Ruffini endings, have demonstrated a better ability to be reinnervated [69]. Unlike with muscle injury, sensibility may be recovered many years after a nerve injury [71].

Clinical classification of nerve injury

In 1941, Cohen introduced a classification to describe the injury to peripheral nerves: neurapraxia, axonotmesis, and neurotmesis. In the early 1940s, Seddon [72,73] examined 650 patients with peripheral nerve injuries and popularized Cohen’s classification system. In 1951, Sunderland [74] expanded upon the classification system by defining five distinct degrees of nerve injury; this is the classification system that is commonly used today. Sunderland’s third- and fourth-degree injuries were included as extensions of axonotmesis and neurotmesis, respectively, in the original classification used by Seddon. In 1988, Mackinnon coined the term “6th degree injury,” which was defined as a mixed injury involving different combinations of injuries [75] (Fig. 13).

A first-degree peripheral nerve injury (neurapraxia) shows recovery within the first 3 months. A second-degree injury (axonotmesis) fully recovers; this occurs at the rate of 1 inch per month. A third-degree injury demonstrates incomplete recovery with the same time course as an axonotmetic type injury. A fourth-degree injury is in continuity, but, like the transected fifth-degree injury, it will not recover. A sixth-degree injury demonstrates a variety of recovery patterns based on the pattern and involvement of the injury.

First-degree injury, neurapraxia

The fundamental basis of a first-degree injury is a conduction block with preservation of anatomical

Fig. 12. Distal glabrous human skin. MC, Meissner corpuscle; MD, Merkel cell-neurite complex; PC, Pacinian corpuscle; SG, sweat gland; SD, sweat duct. (Modified from Mackinnon SE, Dellon AL. Surgery of the peripheral nerve. New York: Thieme, 1988. p. 26; with permission.)

Fig. 13. Schematic diagram representing the six classes of nerve injury. A healthy fascicle is represented where the blood supply of the nerve enters via the mesoneurium. Continuing clockwise, Neurapraxia (I) or loss of axonal myelin is shown. Axonotmesis (II) or second-degree injury is depicted in the next fascicle where loss of myelin and axon has occurred without damage to the endoneurium. The two fascicles (III) depict a third-degree injury. A fourth-degree injury (IV) is shown with damage to all portions of the nerve except for the epineurium. Fifth-degree injury or neurotmesis (V) is defined as complete nerve transection. No recovery is possible without microsurgical repair. A mixed nerve injury, or sixth-degree injury, is a combination of various degrees of nerve injury and is referred to as neuroma in-continuity. (From Winograd J, Mackinnon S. Peripheral nerve injuries: repair and reconstruction. In: Mathis S, Hentz VR, editors. Plastic surgery. Philadelphia: Elsevier and Saunders; 2003; with permission.)
continuity. Although recovery is complete, the time required varies from days to 3 months. There is no nerve regeneration involved in the recovery, and there is no advancing Tinel sign because there is no axonal involvement. Histologically, at most, demyelination is noted. Examples of first-degree injuries include tourniquet palsy or a similar type of localized pressure palsy. In early nerve entrapments, the degree of injury is a first-degree injury with a partial electrical conduction block with prolonged latency measurements.

Second-degree injury, axonotmesis

In second-degree injuries, the endoneurium and perineurium remain intact. A Tinel sign is present and can be traced distally as axonal regeneration occurs. Disintegration of the axon and all the associated changes, collectively referred to as Wallerian degeneration, occur below the site of the injury. The general arrangement of the axon sheaths and the remaining structures comprising the nerve are preserved, as is the integrity of the endoneural tube. Because nerve recovery depends on the regrowth of the axon, structures typically recover in the anatomic order, and the preservation of the endoneural tubes ensures complete restoration of the original pattern of innervation. Nerve recovery should be complete.

Third-degree injury

The structure pattern of third-degree injury involves endoneurial scarring and disorganization within the fascicles. The endoneural tube is disrupted, resulting in erroneous alignment of the regenerating axonal fibers. Regeneration progresses through a component of scar tissue within the endoneurium, thus limiting the regenerating fibers’ ability to make contact with distal receptors or end organs. The rate of recovery after a third-degree injury occurs as expected in axonotmesis, at approximately 1 inch per month. An advancing Tinel sign demonstrates the level of regeneration, but the degree of recovery will not be complete. If the fascicle contains sensory and motor fibers, then a mismatch of motor and sensory fibers can occur, leading to a poorer functional result.

Fourth-degree injury

A fourth-degree injury is a condition in which the nerve is physically in continuity, but regeneration does not occur across scar block. A Tinel sign is found at the level of the injury but does not advance because regeneration is blocked by scar tissue. As in second- and third-degree injuries, Wallerian degeneration takes place in the nerve distal to the injury. If recovery is to occur, then surgical intervention with nerve repair, nerve grafting, or conduit technique is necessary. These injuries are typically the result of a severe stretch, traction, crush, cautery injury, or nerve injection.

Fifth-degree injury, neurotmesis

The fundamental basis of a fifth-degree injury is severance of the nerve trunk. Recovery is not possible without a microsurgical repair. Although these injuries can occur through a severe stretch and resulting avulsion, they are more commonly associated with penetrating trauma.

Sixth-degree injury

In 1988, Mackinnon used the term “sixth-degree injury, neuroma-in-continuity” to describe a mixed nerve injury [75]. She illustrated how the pattern of recovery is mixed respective to the varying degree of injury (I, II, III, IV, V). Partial recovery does occur in fascicles with a third-degree injury, and complete recovery takes place in the fascicles that have a first- or second-degree injury. No recovery is seen in fascicles with fourth- or fifth-degree injury patterns. In this injury, some fascicles may be normal.

The sixth-degree injury is in many ways the most surgically challenging. There is a significant potential for underestimating the overall injury due to limited recovery in the less injured portions of the nerve. A careful assessment and correlation of the observed recovery pattern and fascicular anatomy is indicated. Similarly, careful surgical technique with microinternal neurolysis allows for fascicular separation and individual reconstruction of the fourth- and fifth-degree injuries without injury to the other fascicles.

Compression neuropathy

The pathology found in chronic nerve compression can span the entire range of the nerve injury. In the early stages, nerve compression may be associated with the breakdown in the blood-nerve barrier. It is followed by subperineurial edema with fibrosis and subsequently localized segmental demyelination. Diffuse demyelination and eventually Wallerian degeneration of the nerve fibers occurs in advanced stages. These changes are dependent on the amount and extent of the compressive forces (Fig. 14).
Fig. 14. Schematic diagram outlining the pathogenesis of nerve compression. The initial changes involve the blood-nerve barrier with endoneurial and subperineurial edema secondary to subperineurial edema. Next, changes involve the connective tissue layers that demonstrate increased perineurial and epineurial thickening. Localized nerve fiber changes occur, with some fascicles appearing normal and others demonstrating localized areas of demyelination of the large fibers. Unmyelinated fibers show evidence of regeneration with a new population of small unmyelinated fibers. The central fascicles or the central fibers are usually spared, and progressive compression results in diffuse injury of the myelinated and unmyelinated fibers. (Adapted from Mackinnon SE, Dellon AL. Surgery of the peripheral nerve. New York: Thieme, 1988. p. 42; with permission.)

Nerves with more connective tissue and fewer fascicles may be better protected and undergo neural changes slower than nerves with less connective tissue [76]. Similarly, fascicles located closer to the predominant compression undergo changes sooner than other more distantly located fascicles. Organized fibrosis in the subperineurial space results in the formation of Renault bodies that often occur at sites where the nerve crosses a joint. This is believed to be related to repetitive movement and traction occurring across joints.

Various methods have been described to recreate or induce acute or chronic compression in a peripheral nerve. Rydevik et al [77] used a rabbit tibial nerve to examine the effect of graded compression on the intraneural blood flow. They found that external pressures of 20 mm Hg caused a reduction in venule blood flow, 30 mm Hg resulted in an inhibition of axonal transport, and 80 mm Hg caused a complete cessation of intraneural blood flow [77].

The impact of prolonged nerve compression on function has also been examined. In a rat model, the effects of various pressures (10, 30, and 80 mm Hg) over different durations (4 hours to 28 days) were studied [78]. Within hours, subperineurial edema, inflammation, and the formation of fibrin deposits were reported; within days, fibrous tissue proliferation was present; and fibrosis was seen by 28 days. At higher pressures, (80 mm Hg), axonal damage was evident.

In 1973, Upton and McComas [79] introduced the “double crush” hypothesis. They hypothesized that
proximally located nerve compression could cause distal sites to become susceptible to compression. The authors associated a high incidence of carpal and cubital tunnel syndromes with associated cervical root lesions. Summation of compression along the nerve can lead to changes in axoplasmic flow with subsequent pathology. The concept of double or multiple crush has a clinical relevance in patients who demonstrate multiple levels of nerve compression. Failure to recognize this possible condition results in a failure to relieve the patient’s underlying pathology.

Systemic disease, such as diabetes, thyroid disease, alcoholism, and various arthritic states, can result in peripheral neuropathies and lead to enhanced susceptibility of nerve compression. Dellon et al [80] have demonstrated that, in the streptozocin model, the diabetic nerve is more susceptible to compression. It seems that glucose enters the nerve directly (because there is no blood-nerve barrier to glucose), causing endoneurial edema. The glucose is then metabolized to hydrophilic polyols, which pull additional water into the endoneurial space. The resulting edema leads to increased endoneurial fluid pressure and progresses to myelin changes. It seems that anything that could alter axoplasmic physiology could render the nerve more susceptible to developing a compression neuropathy and act as a “crush.”

Vibration can also result in peripheral neuropathy. A number of studies have shown the association of vibratory exposure with the development of peripheral neuropathy [81–84]. The histologic changes associated with this type of exposure are much like those seen in compression neuropathy, with the development of intraneural edema, demyelination, and eventual axonal loss [85]. Epidemiologic investigations have found a strong association between vibratory exposure and the development of compression at the carpal tunnel [86].

**Improvements in neuroregeneration**

Recently, an enhancement in neuroregeneration with the use of FK506 has been shown after nerve crush, transection, repair, and nerve grafting. Although the exact mechanism of this action is unclear, it seems that its beneficial effects are enhanced at higher doses or with immunosuppressive doses [87–90]. It also seems that the beneficial effects of FK506 are seen even when its administration is delayed [91].

Al-Majed et al [50] have recently shown the application of direct nerve stimulation to increase peripheral nerve regeneration. It is believed that electrical stimulation of the decompressed nerve is beneficial by resulting in a more synchronous regeneration. Nicolaidis and Williams [92] presented some promising work on the usefulness of continuous electrical stimulation via implantable electrodes in deinnervated muscle. In a study of 15 patients with peripheral nerve injuries of the upper extremities, the authors demonstrated improved functionality in all cases with extended stimulation (range of 127 to 346 days).

**Summary**

The response to nerve injury is a complex and often poorly understood mechanism. An in-depth and current command of the relevant neuroanatomy, classifications systems, and responses to injury and regeneration are critical to current clinical success. Continued progress must be made in our current understanding of these varied physiologic mechanisms of neuro-regeneration if any significant progress in clinical treatments or outcome is to be expected in the future. Reconstructive surgeons have in many ways maximized the technical aspects of peripheral nerve repair. However, advances in functional recovery may be seen with improvements in sensory and motor rehabilitation after peripheral nerve surgery and with a combined understanding of the neurobiology and neurophysiology of nerve injury and regeneration.

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