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Pathophysiology of Nerve Injury

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Introduction

In this chapter, the pathophysiology and neurobiology of surgical peripheral nerve disorders specifically related to nerve injuries and compression neuropathies have been discussed. Nerve disorders which require surgical intervention may be caused by several mechanisms, following either direct or indirect injury. The hallmark of direct surgical nerve disorders is traumatic injury, which can be further divided into medium- to high-energy injury (e.g., nerve transection, traction, contusion, or avulsion) and low-energy injury (e.g., compressive neuropathies, compartment syndrome). Indirect peripheral nerve disorders may be caused by thermal, electrical, or radiation injury and other complex nerve injuries related to inflammatory processes (**Flowchart 2.1**).

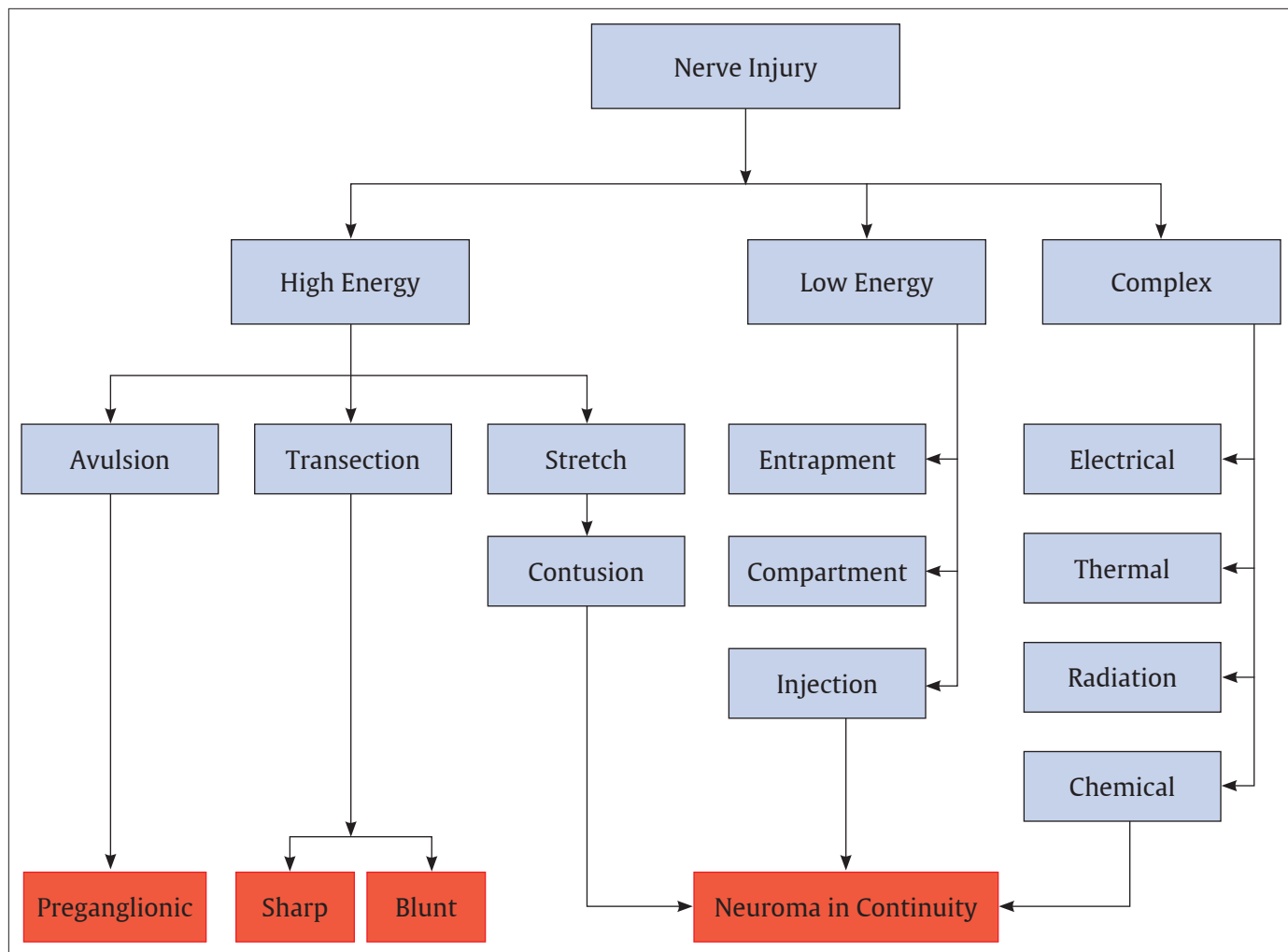
In order to tailor the best management in a timely manner which allows for optimal recovery of nerve injury, it is of utmost importance to appreciate the pathophysiological and regenerative processes related to nerve injuries. In this chapter, these points have been addressed and the consideration related to surgical intervention of peripheral nerve disorders have been explained.

Grading of Peripheral Nerve Injuries

Nerve injuries are graded according to morphological features which also relate to recovery potential and hence reflect on the management of these injuries (**Table 2.1**). Seddon first described three well-defined types of nerve injury: neurapraxia (“transient block”), axonotmesis (“lesion in continuity”), and neurotmesis

(“division of a nerve”).¹ Sunderland further classified nerve injuries in ascending order of severity from the first to the fifth degree with anatomical and functional correlates.² Sunderland Grade I nerve injuries (neurapraxia) are characterized by conduction block without anatomical disruption and no axonal degeneration. Usually, recovery is so fast that it cannot be explained in terms of axonal regeneration (e.g., tourniquet paralysis, Saturday night paralysis, crutch paralysis).¹ Sunderland Grade II nerve injuries (limited axonotmesis) feature axonal discontinuity with preserved arrangement of the endoneurial sheaths and remaining structures, allowing for precise reinnervation. Grade II nerve injuries are expected to experience very good recovery with no or insignificant functional deficit. Sunderland Grade III nerve injuries occur when there is axonal and endoneurial disruption, whereas Grade IV injuries also include perineurial disruption with only the epineurium preserved. Spontaneous functional recovery in Grade III and IV lesions is limited or absent, giving rise to neuroma-in-continuity (NIC).³ These injuries present difficult dilemmas in clinical management due to their occult nature, poor functional outcome owing to reduced muscle reinnervation, and tainted axon regeneration.^{4–6} Grade V Sunderland nerve injuries are characterized by complete nerve transection and are usually associated with laceration wounds; therefore, they are recognized and surgically treated early. Sunderland mixed peripheral nerve injury (Grade VI) presents a variable injury and therefore unpredictable recovery.⁷

Knowledge of specific anatomical muscle innervation and sensory distribution is fundamental for localizing the level of injury and later appreciating the recovery process. Since nerve regeneration occurs



Flowchart 2.1 Mechanisms of peripheral nerve injury. In red are injuries characteristic. Note avulsion and transection injuries will not recover spontaneously due to loss of neuronal continuity and most definitely will require microsurgical reconstruction. Other injuries result in neuroma-in-continuity with variable degree of recovery dependent on the grade of injury and proximity to the target.

Table 2.1 Peripheral nerve injury grading

Sunderland grade	Seddon grade	Disrupted elements	Expected recovery ^{a,b}
I	Neuropraxia	Conduction block +/- myelin injury	Complete
II	Axonotmesis	Grade I + axons disruption	Excellent/good
III		Grade II + endoneurium disruption	Variable
IV		Grade III + perineurium disruption	Variable/poor
V	Neurotmesis	Grade IV + epineurium disruption	None
VI		Mixed injury	Poor

^aExpected recovery without surgical intervention.

^bRegeneration period with or without surgical repair is 1 mm/day.

from the injury site distally, signs of recovery, whether spontaneous or following nerve reconstruction, appear in anatomical order where a regular march of recovery in muscles is often observed. When managing surgical nerve disorders, it is important to be familiar with both surgical (surface) and functional anatomy.

Mechanisms of Nerve Injuries

Mechanisms of nerve injuries are listed in **Box 2.1**.

Direct Nerve Injury (Trauma)

Traumatic injury of the peripheral nervous system represents a major cause of morbidity and disability which subsequently causes a substantial economic and social burden. Peripheral nerve injuries have been estimated to affect 2.8% of all trauma patients, many of whom acquire lifelong disability.⁸

Direct blows applied over the neurovascular structures and the degree of biomechanical forces exerted per surface area will produce variable degree of nerve injury depending on the amount of energy exerted and the characteristics of the applied force (sharp vs. blunt). Injuries such as transection, contusion, stretch, and avulsion are generally sustained when medium-to high-energy forces are applied directly to nerves, whereas injuries such as compressive neuropathies tend to occur when nerves are subjected to chronic or repetitive low-energy forces. Indirect nerve injuries from radiation and thermal energy involve rather heterogeneous combination of different injuring factors and they can be grouped together as complex group of nerve injuries.

Medium to High Energy

Transection: Soft-tissue lacerations with objects such as knives, glass, propeller and fan blades, chain saws, auto metal, and surgical instruments may sharply transect nerves in about 30% of cases.^{9,10} The extent of functional loss varies from mild and incomplete to severe and total. If a nerve is partially transected, the injury to those fibers cut is, by definition, neurotmetic or Sunderland Grade V. On the other hand, those fibers not directly transected can have a variable degree of injury and be Sunderland Grade II, III, or IV

Box 2.1 Mechanisms of nerve injuries.

- Direct nerve injury (trauma)
 1. Medium to high energy
 - (a) Transection
 - (b) NIC (stretch, traction, and contusion)
 - (c) Avulsion injury
 2. Low energy
 - (a) Entrapment neuropathies
 - (b) Compartment syndromes
 - (c) Injection
- Indirect nerve injury (complex nerve injuries)
 1. Electrical
 2. Thermal
 3. Irradiation
 4. Chemical

(**Fig. 2.1A, B**).² In humans, the partially transected portion of a nerve seldom regenerates spontaneously and when they do it is not sufficient to restore function and therefore often needs microsurgical repair.¹¹ Functional recovery in some of these cases can be attributed to reversal of neurapraxia or regeneration in the bruised and stretched portion of the nerve rather than in the transected portion.

The physical appearances of both the totally transected nerve and nerve that has sustained blunt transection change over time. Following sharp transection, the epineurium is cleanly cut, and there is minimal contusive injury or hemorrhage in either stump. With time, the stumps of the cleanly cut nerve retract and become enveloped in scar. The amounts of proximal neuroma and distal nerve stump scarring are much less compared with those formed in a more contusive or blunt transection. Blunt transection is associated with a ragged tear of the epineurium acutely and an irregular, longitudinal extent of damage to a segment of the nerve. Bruising and hemorrhage can extend for several centimeters up or down either stump. Retraction and proliferative scars around the stumps are often more severe than those that are seen with sharp transection.¹²

Management of transection nerve injury (Grade V) will in most cases require microsurgical repair for removal of the injured and scarred tissue and reconstruction of nerve continuity, by either an end-to-end suture or a nerve graft.

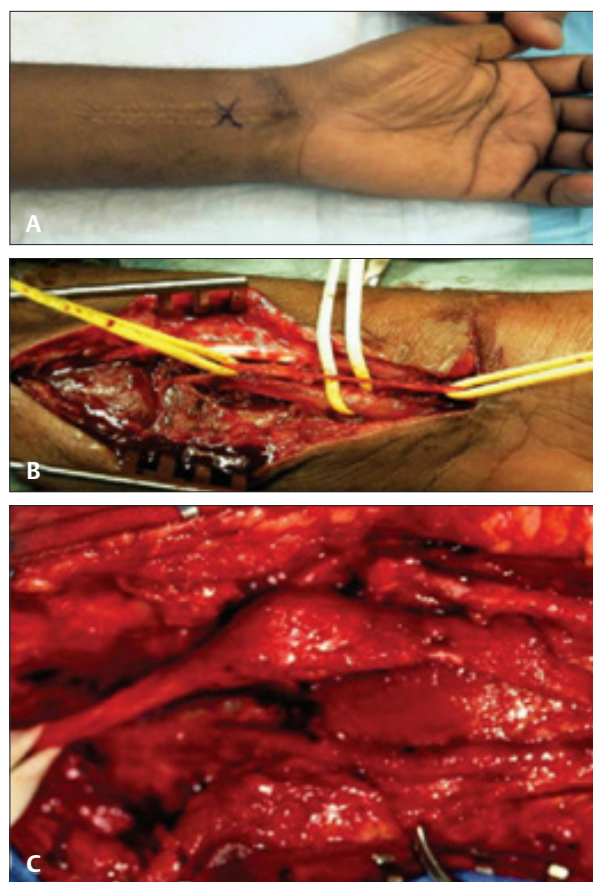


Fig. 2.1 This patient sustained a complex laceration of the distal part of the forearm and wrist area from a penetrating glass injury 2 years prior to the most recent presentation. She underwent exploration and debridement of the acute injury and repair of the soft-tissue injuries by a plastic surgeon. From the outset, the patient was aware of sensory alterations in the palmar thenar area, a region in which she started experiencing severe allodynia. The numbness in her thumb and index finger slowly resolved over time. She continued to have some persistent weakness in the thumb and on examination had noticeable atrophy and Grade III function in the abductor pollicis brevis muscle. Her main concern, however, was a very painful and tender area overlying the distal part of the longitudinal aspect of the scar, marked with an “X” in (A) At surgical exploration (B), there was a lateral neuroma affecting the main median nerve (encircled with a white vessel loop) and a more substantial injury in continuity involving the palmar cutaneous branch of the median nerve (encircled with two yellow vessel loops). The palmar cutaneous branch was resected widely. We elected not to repair the partial main median nerve injury because the patient actually already had very serviceable hand function. The patient had excellent pain relief postoperatively and in long-term follow-up. This case illustrates that even with a sharp penetrating injury, the nerve may be incompletely lacerated or not lacerated at all. Neuroma in continuity of the radial nerve (C) adjacent to the spiral groove is shown in a patient who suffered a proximal humeral shaft fracture. The very displaced fracture had previously been managed by open reduction and internal fixation, which resulted in solid bony union. The patient continued, however, to manifest complete radial nerve palsy over a period of several months in follow-up. The finding at surgery was a large neuroma-in-continuity involving the radial nerve. The neuroma failed to conduct a nerve action potential, so graft repair was undertaken after resecting the lesion.

Adapted from: Gordon T, Sulaiman W, Midha R. Pathophysiology of surgical nerve disorders (Peripheral Nerve Section editors: A Filler, E Zager, and D Kline). In: Youmans Textbook of Neurological Surgery, 6th ed (R. Winn, editor). Elsevier, 2011.

Neuroma-in-continuity (stretch, traction, and contusion): Medium- to high-energy forces applied to nerves can result in a combination of different types of serious nerve injuries owing to significant tissue traction and contusions.¹³ The perineurium of intact nerves is rich in elastin and collagen, which endow

tensile strength.¹⁴ However, even 8% stretch leads to a disturbance in intraneural circulation and blood–nerve barrier function,¹⁵ while stretch beyond 10 to 20%, especially if applied acutely, results in structural failure.¹⁶ Such forces can therefore occasionally distract a nerve, pulling it totally apart, or more commonly leave

it in continuity but with considerable internal damage (**Fig. 2.1C**). If distracted by substantial forces, the nerve becomes frayed, and both stumps are damaged over many centimeters with severe retraction and scarring about both stumps.

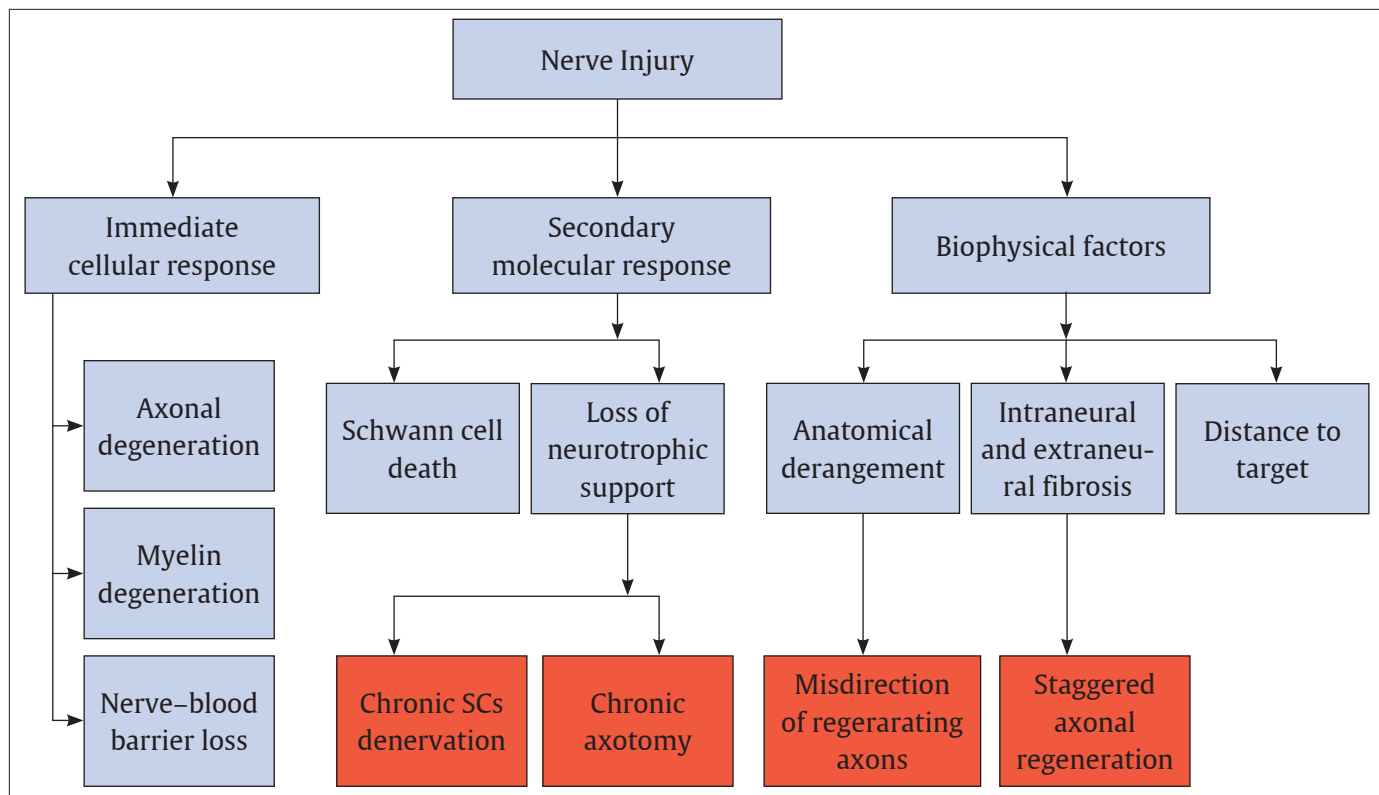
Often the nerve is left in continuity where the epineurium retains its integrity, but the degree of intraneural damage is variable and presents a spectrum of internal nerve fiber damage. A stretch mechanism is also responsible for segments of damage to nerve displaced by high-velocity missiles, especially with gunshot wounds.^{12–14,17} Traction forces applied to nerves are commonly sufficient to tear apart the intraneural connective tissue structure as well as to disconnect axons.¹⁸ Such lesions are Sunderland Grade IV and are essentially neurotmetic despite physical continuity of the nerve.¹⁹ Less frequently, such forces result in a more axonotmetic or Sunderland Grade II or III lesion which may have the potential for effective regeneration because of less connective tissue disruption.²

Most nerve injuries leave the nerve in continuity which can make the determination of the degree of nerve injuries and prognostication of functional recovery quite difficult. Contusive lesions tend to leave the nerves in continuity although the vasculature may be damaged. These lesions in continuity can be either focal or diffuse, and may even be multifocal with intervening areas of seemingly intact nerve. In the diffuse subtype, which represents the majority of the cases, the entire cross section of the nerve has a similar extent of internal damage.²⁰ Clinical and electrophysiologic examinations provide guidance as to the completeness of the injury to the nerve fibers such that sparing of one or more fascicles may produce partial neurological deficits and preserved, but diminished, nerve action potentials (NAPs) across the injury site.^{21,22}

With the typical lesion in continuity, the nerve is acutely swollen, with extravasation of serum or blood, while internally axons and their myelin coverings disintegrate, and there is disruption of the connective tissue elements.^{23,24} Wallerian degeneration occurs, and axonal and myelin debris is phagocytosed from both the injury site and more distal nerve.²⁵ The Schwann cells (SCs), basal lamina, and distal connective tissue elements survive and are well positioned and conducive for axonal outgrowth.²⁶ Unfortunately,

the endoneurial and perineurial elements at the injury site rapidly proliferate and lay down poorly structured collagen, as well as other potentially inhibitory matrix molecules such as chondroitin sulfate proteoglycans (CSPGs), interfering with organized and properly directed axonal regeneration.²⁷ Because there is also some retrograde damage proximal to the injury site with most nerve injuries, clusters of regenerating axons must first traverse this area of loss.²⁸ These regenerating axons next encounter poorly restructured collagen and CSPGs at the injury site, leading to further disorganization in their orientation and delay in the process of axonal regeneration (i.e., staggered axonal regeneration).^{29,30} Axons branch many times as they traverse the site of injury. Such axonal branching in the human body may occur several hundred times.³¹ Other axons may be deflected into peripheral connective tissue layers at the injury site as well as distally. As a result, axons reaching the distal stump are thin, poorly myelinated, and therefore less likely to reach original distal end-organs than with a more axonotmetic injury. Many severe lesions in continuity are therefore not capable of regeneration of a quality to lead to recovery of useful distal function. Therefore, recovery following severe peripheral nerve injury with nerve continuity is often unsatisfactory.¹⁰ This undesirable outcome is believed to be related to the process of axonal attrition and misdirection following nerve injury with anatomical disruption of the nerve tissue.³² Some of the complex interrelating factors that ultimately determine the success of axonal regeneration after nerve injury are outlined in **Flowchart 2.2**. In clinical practice, because it is difficult to discern the extent of internal damage after this type of injury, most lesions in continuity are therefore clinically followed and reevaluated at intervals for a few months before surgical exploration (**Table 2.2**).³³

Avulsion injury: Brachial plexus injury is a common disorder resulting from a stretch mechanism. Stretch or traction injuries to the plexus most commonly result from extremes of movement at the shoulder joint, with or without dislocation or fracture of the humerus or the clavicle. With blunt or traction forces, scapular, rib, or cervical spine fracture, or any combination of these, can also occur.^{8,34} A clavicular fracture



Flowchart 2.2 Factors affecting neuronal regeneration after nerve injury. Note, in red are common pathways directly responsible for poor regeneration. Axonal attrition as a result of chronic SCs denervation and chronic axotomy together with misdirection and staggered axonal regeneration will ultimately hinder on the full potential of neuronal recovery.

seen with brachial plexus injury does not indicate that the injury was caused by the fracture but rather attests to the extensive force applied to the shoulder joint or directly over the clavicle (e.g., seat belt injury). On rare occasions, however, compressive upper trunk plexopathy may result in a delayed fashion, from bony callus generated from clavicular malunion (**Fig. 2.2**).³⁵ Either upper or lower elements of the plexus may suffer the predominant injury, or with severe traction forces, all elements may be involved in addition to the phrenic nerve and even subclavian vessels. All grades of damage are possible. Spinal nerves and roots can be avulsed from the spinal cord or more laterally from truncal or more distal outflows. The stretched elements may be left in continuity and have a mixture of neurapraxia and axonotmesis. A combination of neurapraxia, axonotmesis, and neurotmesis may coexist but unfortunately these mixed grades of injuries are more commonly severe in degree, having significant neurotmetic components.

Some anatomical features of the brachial plexus may predispose it to traction or even rupture. After the roots penetrate the dura, they become spinal nerves. The spinal nerves run in the gutters of the foramina in the corresponding vertebrae. At this intraforaminal level, the nerves are relatively tethered by mesoneurial-like connections to the gutters.³⁶ The spinal nerves then angle inferiorly to appear between the scalenus anticus and scalenus medius muscles and thus gain entrance to the posterior triangle of the neck. Spinal nerves are often injured in a characteristic fashion just as they run off the lip of the gutter of the transverse process. Forces here may distract spinal nerve from trunk, producing a rupture or avulsion of the rootlets from the spinal cord (**Fig. 2.3**). Alternatively, they may produce severe intraneural damage resulting in lengthy lesions in continuity that not only involve spinal nerves and trunks but also may extend into the divisions and rarely even into the more distal infraclavicular elements. A common finding with severe stretch

Table 2.2 Suggested management paradigm for peripheral nerve injuries

Complete sharp transection (e.g., iatrogenic injury, clean stab wound)
Microsurgical repair in the acute phase (immediate 3 days)
End-to-end coaption without applying tension
Autologous nerve graft may be rarely needed to bridge gap if tension-free repair not possible
Complete blunt transection (e.g., some stab wounds, propeller and fan blades, chainsaw injury)
Microsurgical repair within 2 to 4 weeks
Debridement of injured nerve tissue and reconstruction of nerve continuity
Most often autologous nerve graft is needed to bridge gap
May require preoperative imaging (MRI/US) to evaluate degree and level of injury
NIC complete neurological loss (e.g., fracture, gunshot wound, iatrogenic insult)
Monitor with close clinical and electrophysiological studies for 2 to 3 months
Explore if no significant neurological or electrical improvement occurs
Microsurgical removal of fibrotic tissue and neuroma and reconstruction of nerve continuity
Use intraoperative stimulation and NAPs to decide for or against resection
NIC incomplete neurological loss with significant distal sparing
Most patients improve during close observation
Monitor with close clinical and electrophysiological studies for 2 to 3 months
Surgical intervention may still be required if:
expanding masses (hematoma, pseudoaneurysm) with clinical worsening lesion near an entrapment site (e.g., peroneal nerve at the lateral aspect of the knee)
No further significant recovery occurs with major neurological impairment
Neuropathic pain not amendable to pharmacotherapy and physiotherapy
Avulsion injury or proximal NIC injury (e.g., motor vehicle accident, fall injury with traction)
Monitor with close clinical and electrophysiological studies for up to 3 to 4 months
Explore if no significant neurological or electrical improvement occurs
Need of preoperative imaging (MRI/US/myelography) and electrophysiology
Use intraoperative stimulation and NAPs/SEP/MEP to decide for or against resection
Nerve transfer procedure may be favored alternative to nerve grafts (often both tactics used)

Abbreviations: MEP, motor-evoked potentials; MRI, magnetic resonance imaging; NAPs, nerve action potentials; NIC, neuroma-incontinuity, SEP, sensory-evoked potentials; US, ultrasonography.

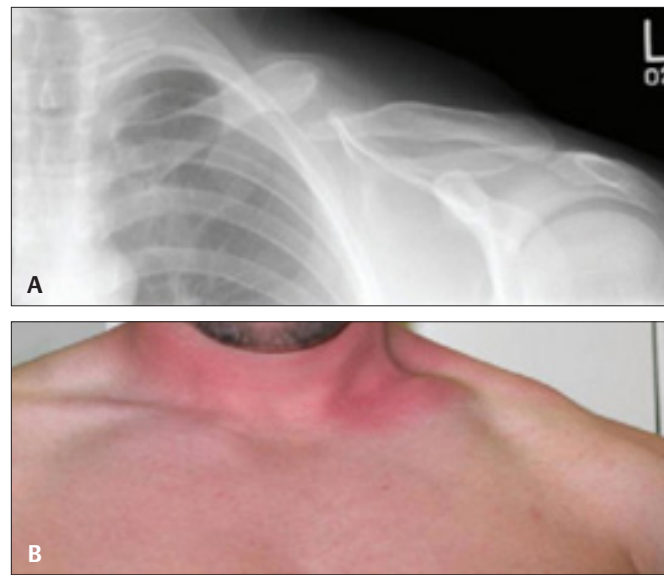


Fig. 2.2 This patient had sustained a displaced left clavicular fracture 3 years before clinical evaluation by a neurosurgeon. He initially had no neurological deficit. About 2.5 years after the injury, he started to notice paresthesia in his shoulder girdle emanating from the supraclavicular area and, over the course of time, became aware of progressive weakness in shoulder abduction. Physical examination confirmed a severe suprascapular neuropathy and mild weakness in deltoid function. Electromyography demonstrated evidence of denervation that was severe in the supraspinatus and infraspinatus and sparse, although active in the deltoid. **(A and B)** Radiographic and clinical appearance of the nonunited midclavicular fracture with substantial callus formation. The patient underwent exploration and external neurolysis of the upper part of the trunk along with the suprascapular and posterior division branches from the trunk that were being impinged by the callus. The callus was resected widely and the fracture repaired by an orthopedic surgery colleague with a plate and lag screw. The patient eventually achieved excellent bony union of the site and progressive improvement in shoulder girdle muscle strength and function. This case illustrates delayed complication from a nonunited fracture with callus causing adjacent nerve compression. **Adapted from:** Peripheral Nerve Section Editors- A Filler, E Zager and D Kline). In: Youmans Textbook of Neurological Surgery, 6th Edition (R Winn, Editor), Elsevier, 2011.

injuries is to see cords pulled away from more proximal elements of the plexus such as roots and trunks. Unfortunately, under these circumstances, intraneural damage on these proximal elements often extends close to, if not all the way to, the spinal theca or cord.³¹

Despite the specific anatomic relationships of the brachial plexus elements, most traction injuries do not avulse or pull apart the plexus elements. Instead, the elements are left in some continuity but have a severe degree of internal disruption, essentially a Sunderland Grade IV injury. Each plexus element may have a different grade of damage within the same injury zone. In such cases, the lesion is not focal but extends over several centimeters of nerve. When avulsion does occur, traction forces along the axis of the brachial plexus literally tear their rootlets out of the spinal cord, resulting in a preganglionic injury (**Fig. 2.3D**).

Brachial plexus avulsion injury with preganglionic disruption should be recognized early for better prognostication and management of these injuries. Pre- and postganglionic injuries pose different clinical features and hence different management scheme; avulsion injury includes those which are preganglionic, whereas postganglionic injuries are considered as NIC or transection (rupture) injury. A key clinical feature of avulsion injury is that because of the disruption at the level of the spinal cord, these types of injuries pose an especially difficult challenge. If the major injury is neurotmetic, it can involve such a long segment of the nerve so that the only operative method for replacing the resulting extensive neuroma is use of lengthy grafts. The results of repair with such lengthy grafts are often poor, and these are especially prone to failure at the proximal levels where many stretch injuries begin.

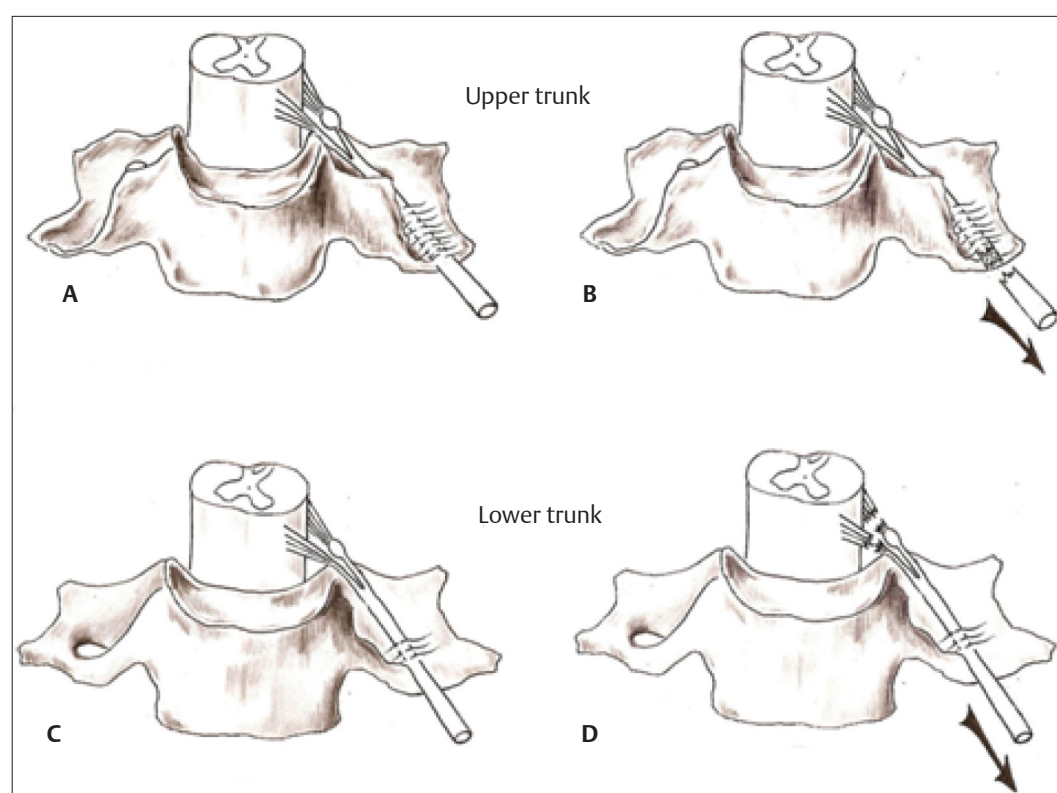


Fig. 2.3 Severe distracting forces can result in nerve stretch injury or even avulsions depending on local anatomical factors. Note that lower trunk spinal nerves are prone to preganglionic injury. The bony “chutes” of the lower trunk spinal nerves are abbreviated when compared to those transmitting the upper trunk spinal nerves (**A and B**), and the lower trunk spinal nerves traversing these bony “chutes” are less bound to the bone by connective tissue (**C and D**). Consequently, the C8 and T1 nerves are prone to preganglionic injury (**D**), whereas the spinal nerves (C5 and C6) contributing to the upper trunk tend towards postganglionic injury (**B**). (From: Yang LJ-S, McGillicuddy JE. Lower trunk brachial plexus palsy. In: Midha R, Zager E, eds. *Surgery of Peripheral Nerves: A Case Based Approach*. New York, NY: Thieme; 2008:14–17.

Therefore, surgical treatment for avulsion injuries and now also many of the extensive proximal stretch injuries mainly consists of nerve transfers and muscle or tendons transfers depending on the function of adjacent levels and timing for surgical intervention.^{37,38}

Low Energy

Entrapment neuropathies: Peripheral nerve, like other neural tissues, is critically dependent on blood flow and continuous nutrient delivery. Since mechanical nerve compression also simultaneously affects its vasculature and blood supply, the relative roles of ischemia and physical deformation in compression lesions remain unsettled.³⁹ Recent evidence suggests that although ischemia may be primarily responsible for a mild type of rapidly reversible nerve lesion,

direct mechanical distortion is the major factor underlying more severe, long-lasting forms of pressure palsy such as Saturday night palsy or tourniquet paralysis.^{40–42} Ischemia can produce a wide range of nerve fiber lesions and, if severe and prolonged, results in widespread axonal loss and Wallerian degeneration.⁴³ Studies on limb ischemia suggest that there is a critical period of approximately 8 hours, after which irreversible nerve injury ensues.⁴⁴ Chronic repetitive compression and ischemic events will ultimately cause fibrosis which can exacerbate nerve ischemia, creating a vicious circle. In order to mitigate this aggravating effect, a decompressive procedure, that is, neurolysis, may be warranted.

One of the major concerns with a neurolysis procedure is fibrotic response and scar tissue formation

following the surgical intervention as part of the normal tissue healing. Therefore, it is of utmost importance to minimize postoperative fibrosis by reducing perineural tissue damage and aim to preserve all vascular structures.

Recent studies, mainly by Gupta et al, further illustrated the key role of SCs following chronic nerve compression injury in the development of neuropathy.^{45,46} These findings suggest that SCs are key players in the pathogenesis of chronic compression injury, rather than direct axonal damage and subsequent Wallerian degeneration as in more acute nerve injuries. These studies propose intrinsic differences between the pathogenesis of acute nerve injury and chronic nerve compression injury, which is primarily an SC-mediated injury state. Chronic compression of nerve fibers appears to produce myelinated nerve fiber changes that are unique to this mechanism.^{47,48} These include alterations in paranodal myelination, axonal thinning, and segmental demyelination.^{49–52} Axonal injury and therefore Wallerian degeneration result from more severe and/or more sustained degrees of compression.

The degree of recovery after compression or ischemic injury may be accurately predicted in some clinical situations. The characteristic Saturday night palsy results from compression of the radial nerve against the humerus. Total radial nerve palsy often results, but there is return of motor and sensory function in the majority of cases without any need for surgical intervention. Most palsies associated with unconsciousness due to anesthesia and poor positioning or pressure during operation as well as those related to improper application of plaster casts carry a good prognosis for spontaneous recovery.⁵³ There are, however, important exceptions. Sometimes the compression or crushing injury has been severe enough or prolonged enough to cause damage that is irreversible unless operative repair is done. The brachial plexus and the ulnar, sciatic, and peroneal nerves are most commonly affected by these more severe compressive etiologies.⁵⁴ Restoration of function after acute compression and ischemic injury may be less certain in some other circumstances. It may be difficult, for example, to predict the degree of recovery that follows evacuation of hematomas or relief of aneurysmal

compression of such structures as the brachial plexus and the femoral or sciatic nerves.⁵⁵

Compartment syndromes: Severe crush injury, burns, skeletal fracture with vascular compromise, and anticoagulant administration, resulting in hemorrhage, can lead to increased pressure within a fascial compartment. As a consequence of this, severe compression and ischemic damage to peripheral nerves as well as other soft tissues can result. A closed compartment syndrome with impending ischemic paralysis requires immediate decompression with properly placed and usually extensive, longitudinal fasciotomies.⁵⁶ Delay in treatment results in ischemic infarction of muscle, nerve, and other tissues, leading to contractures and other crippling deformities.

Volkmann's contracture is a serious example of ischemic compression due to development of compartment syndrome. There is injury to the brachial artery along with diffuse segmental damage to the median nerve and volar forearm muscles. The large median and sometimes radial nerve fibers serving motor and proprioceptive function are more severely involved than the smaller pain fibers. Electromyography may aid in diagnosis by showing temporary but repetitive and spontaneous motor discharges from muscles most distal to the injury site.⁵⁷ Swelling of the forearm resulting in a painful paresthetic hand must alert the physician to an impending compartment syndrome long before more obvious signs of vascular compromise are apparent.

Ischemia of sufficient magnitude to produce Volkmann's contracture results in severe endoneurial scarring over so long a segment of the median nerve as to make spontaneous regeneration unlikely. In addition to the median nerve, the radial and even occasionally the ulnar nerve may be involved because of a severely swollen elbow and forearm, particularly if the contracture was initially associated with multiple contusive injuries at these levels. Compression of the median nerve must be relieved surgically, especially in the region of the pronator teres and flexor digitorum sublimis muscles.

In summary, extension of neural injury by compression and ischemia is a serious possibility if enough

soft-tissue swelling or an aneurysm, fistula, hematoma, or arterial insufficiency occurs in a relatively closed or confined neurovascular compartment. These lesions are particularly apt to occur with perforating wounds that involve arteries and with fractures but can also be caused by blunt or contusive trauma. Neural damage usually is preventable by expeditious decompression, but it becomes irreversible if severe ischemia involves a long segment of nerve and/or persists for too long a period of time.

Injection: Injection injury is usually an iatrogenic injury caused by a needle placed into or close to a nerve, and damage results from neurotoxic chemicals in the agent injected. The extent of damage varies, depending not only on the agent injected but also on whether the needle and therefore the toxic agent were placed in or close to nerve. There are cases in which some or all of the injury relates to the mechanical damage caused by the needle placement itself. Experimentally, damage from injection seems to require placement of the agent either within the epineurium or, for more serious damage, at an intraneural location, either intrafascicular or in the connective tissue layers between the fascicles.⁵⁸ In humans, however, about 10% of patients subsequently found to have an injection injury have a delay of hours or even days before the onset of symptoms.⁵⁹ This suggests either a purely epineurial locus for deposition of the agent in these cases or placement of medication close to nerve or in a tissue plane from which the agent can gravitate to and bathe the nerve.

The pathology of injection injuries also varies depending on the injection site and the agent injected.⁶⁰ The principal pathogenetic mechanism, however, is necrosis.⁶¹ With intraneural injection, there is acute edema and inflammatory changes with necrosis, which affects connective tissue elements, axons, and myelin.⁶² With time, connective tissue proliferation may occur and produce intraneural scarring, thereby thwarting effective axonal regeneration.⁶³ The blood-nerve barrier at both the perineurial and endoneurial capillary levels are severely disrupted,⁶⁴ a finding that may occur despite preservation of the fascicular structure. After the first few days, the injected segment is no longer swollen and may, with further time, appear

shrunk or even as a segment of nerve with normal diameter. On gross inspection, with or without magnification, the nerve usually appears to have excellent physical continuity. Some agents injected into epineurium or adjacent to nerve produce more proliferation of inflammatory tissue response and scarring than at an intraneural location, but necrosis at the latter is especially damaging and difficult for the regenerative process to overcome spontaneously.

In the usual clinical setting, needle placement results in an electric-like shock down the extremity, followed by or concomitant with a severe burning pain and paresthesias as the agent is injected. Acute symptoms are variously described but are usually severe. With delayed onset, which seems to occur in about 10% of patients with injection injuries, the symptoms are less dramatic but nonetheless bothersome.⁵⁹ These include a burning pain, paresthesias, and radiation of a deep discomfort down the limbs in the distribution of the involved nerve. It is worth mentioning that most common neural injection sites are the sciatic nerve at the buttock level and the radial nerve in the lateral upper arm.^{59,65} Nonetheless, besides sciatic and radial nerves, injection injuries involving almost every other major nerve in the body such as injuries to femoral and lateral femoral cutaneous nerves as well as ulnar and median nerves at wrist, elbow, and upper arm levels have been described.

Although the deficit in neural function usually is caused by intraneural neuritis and scar tissue rather than extraneural scarring, some authors believe that external neurolysis for this complication can reverse loss of function.⁶⁶ We do not agree with this; however, a lesion with partial loss of function and severe pain not responding to analgesics may be helped by internal neurolysis on a delayed basis. An occasional patient may have a true causalgia after injection, and may benefit from sympathectomy, especially if recurrent sympathetic blocks have provided temporary relief.

If the nerve deficit is partial, expectant treatment is best, provided pain is not a severe problem, but if the deficit is complete after several months of observation, exploration becomes warranted. In this regard, if an injection injury to the sciatic nerve spares either the peroneal or tibial division but is complete in the other

division, it is a complete lesion of one division, and this division may need resection and repair if function is to be regained.⁶⁷ A reasonable management approach with injection injuries is to explore the nerve that shows little or no function after 12 to 16 weeks and attempt to evoke an NAP through the injury.⁵⁹ Most lesions have a recordable NAP, but if no response is recorded, the lesion must be resected and repaired in a hope to regain function.

Indirect Nerve Injury (Complex Nerve Injuries)

Electrical: Electrical injury by passage of a high current through a peripheral nerve usually results from accidental contact of the extremity with a high-tension wire causing diffuse nerve and muscle damage.^{68,69} Pathologic reports of peripheral nerve damage caused by this mechanism are sparse, and guidelines for treatment are controversial.⁷⁰ Conservative management of the nerve injury itself and early orthopedic reconstruction of the extremity seem to be best.⁷¹ Prognosis with most low-voltage injuries is excellent, but quite variable for high-voltage injuries.⁷¹ Resection of a lengthy segment of damaged nerve and repair by grafts are usually necessary. Histologically, the segment of the nerve is virtually replaced, first with necrosis and then with connective tissue reaction, including a severe degree of both perineurial and endoneurial scar tissue. Fascicular outline may be preserved, but intrafascicular damage and fibrosis can be severe enough to prevent any but fine and functionally fruitless axon regeneration.

Thermal: Although not a common mechanism of peripheral nerve injury, thermal injury by flame, steam, or hot elements can result in neural damage ranging from a transient neurapraxia to severe neurotmesis with extensive necrosis of nerve as well as adjacent tissues. In patients with circumferential burns, neural damage may be related to delayed constrictive fibrosis, resulting in a tourniquet effect and compartment syndrome. Patients with severe burns involving nerve present with complete motor and sensory loss. The clinical examination is often difficult because of associated soft-tissue injuries, extensive skin loss, and often a massively swollen extremity. In thermal injury, whether by direct effect or secondary to constrictive

fibrosis, long lengths of nerves are often involved, necessitating nerve grafts. The prognosis for functional recovery is poor in such cases, especially if there is also extensive involvement of muscle and other soft tissues.

Irradiation: This is a relatively rare cause of iatrogenic nerve injuries when compared to injection injuries. The irradiation usually affects the brachial plexus but can also occur at the level of the pelvic plexus.⁷² Extensive scar formation in surrounding soft tissues and severe intraneural changes, consisting of myelin loss, axonal degeneration, and extensive endoneurial fibrosis, often result.⁷³

Neurobiology of Peripheral Nerve Injury

In order to understand the paradigms underlining surgical management of nerve disorders, one should appreciate the cellular and biochemical mechanisms of nerve regeneration.

Immediately following peripheral nerve injuries, complex cell-molecular interactions and biomechanical features are essential for nerve regeneration and subsequently successful functional recovery. Significant advancements have been made in the technique of microsurgery of injured nerve which often results in improved outcome for patients. However, recovery of function can be suboptimal in some patients despite the capacity of the peripheral nervous system to regenerate axons. This dichotomous observation has been studied experimentally by several groups, but most elegantly by Tessa Gordon and her colleagues. Key biomolecular factors that have been shown to be responsible for this observation include neuronal attrition, represented by chronic axotomy and chronic SC denervation, together with misdirection of the regenerating axons (**Flowchart 2.2**). In humans, injured neurons regenerate at the slow rate of 1 mm/day. At this rate, reestablishment of a functional motor unit or sensory reinnervation may take months or even years.^{14,74,75} Failure of functional recovery was generally attributed in the past to atrophy of the denervated muscles and sensory organs; however, recent experiments provide strong evidence that failure of functional recovery after microsurgical repair is

mainly attributed to the process of neuronal attrition and misdirection.^{32,76–83}

Regenerative Response after Nerve Injury

Initial phase of regeneration: After nerve injury, the proximal and distal stumps of the injured nerve undergo structural and molecular changes in preparation for the process of axonal regeneration. The proximal stump undergoes dieback degeneration up to at least the first node of Ranvier and then each injured axon elaborates multiple daughter axons.^{84,85} Many of the daughter axons are pruned and those that remain begin the process of elongation through the distal nerve stumps and constitute regenerating units.²⁸ This initial stage of axonal regeneration is sustained both by the availability of locally produced cytoskeletal materials and on neuronally produced and anterogradely transported cytoskeletal proteins such as actin and tubulin.^{85–88}

The distal nerve stumps of severed nerves undergo a degenerative process named after Augustus Waller, *Wallerian degeneration*. It is now understood that Wallerian degeneration is an essential preparatory stage of the process of axonal regeneration via which molecules that could be inhibitory to regeneration (such as myelin) are eliminated.

Axon regeneration proceeds at a rate of 1 to 3 mm/day, the rate corresponding with the slow rate of transport of the cytoskeletal materials. Further elongation and regeneration through the distal nerve stump is dependent on the growth-supportive milieu provided by the SCs of the distal nerve stumps. Lack of an SC-laden endoneurial channels (bands of Büngner) results in misdirected regeneration and formation of neuromas.^{14,89–91}

Role of Schwann cells in axonal regeneration: SCs play a major role in the process of Wallerian degeneration by way of phagocytosis of the axonal and myelin debris. They also secrete chemoattractive factors such as interleukin-1 and monocyte chemoattractant protein-1 that recruit macrophages into the denervated distal nerve stumps which contribute even more significantly to the phagocytosis of axon and myelin debris.^{88,92,93}

Immediately after a nerve is injured, loss of axonal contact triggers the SCs to proliferate and switch their phenotype from a myelinating to a nonmyelinating growth-supportive phenotype.^{87,88,94} The mRNA expression of myelin-associated proteins such as P0 and myelin-associated glycoprotein are downregulated and neurotrophins (viz., nerve growth factor, brain-derived neurotrophic factor, and glial-derived neurotrophic factor) and their receptors (viz., p75, GFRA-1, GFRA-2) as well as adhesion molecules (e.g., neural-cell adhesion molecule) are upregulated in preparation for the process of axonal regeneration (**Fig. 2.4A**).^{87,91,95,96} These upregulated genes are collectively called regeneration-associated genes (RAGs). The change in the gene expression within the SCs and myelin and axonal degeneration and clearance are key features of the process of Wallerian degeneration.^{87,88,94}

Likewise, neurons whose nerves have been injured downregulate mRNAs of proteins required for neurotransmission and upregulate those for rebuilding their peripheral processes.^{80,87,97} Hence, actin, tubulin, and GAP-43 are upregulated immediately after injury.^{87,97} However, the upregulation of RAGs is not sustained in either the injured neurons or the SCs such that by 6 months in experimental animals, most of the upregulated mRNAs are downregulated, thereby losing the growth-supportive environment for regenerating axons (**Fig. 2.4B**).^{96,97} The implication of the time-limited upregulation of RAGs is demonstrated in the progressive decline in the capacities of injured neurons to regenerate their axons and of SCs to support regenerating axons as the duration of nerve repair is prolonged (**Fig. 2.4C**).

Pathophysiological Basis of Surgical Management for Nerve Injuries

Treatment of peripheral nerve injuries requires a broad multidisciplinary approach during the evaluation phase and surgical intervention and also through the recovery period, involving cooperative care from neurology, radiology, rehabilitation, and a dedicated surgical team with expertise in peripheral nerve surgery. Understanding the pathophysiological principles involving nerve regeneration and appreciating

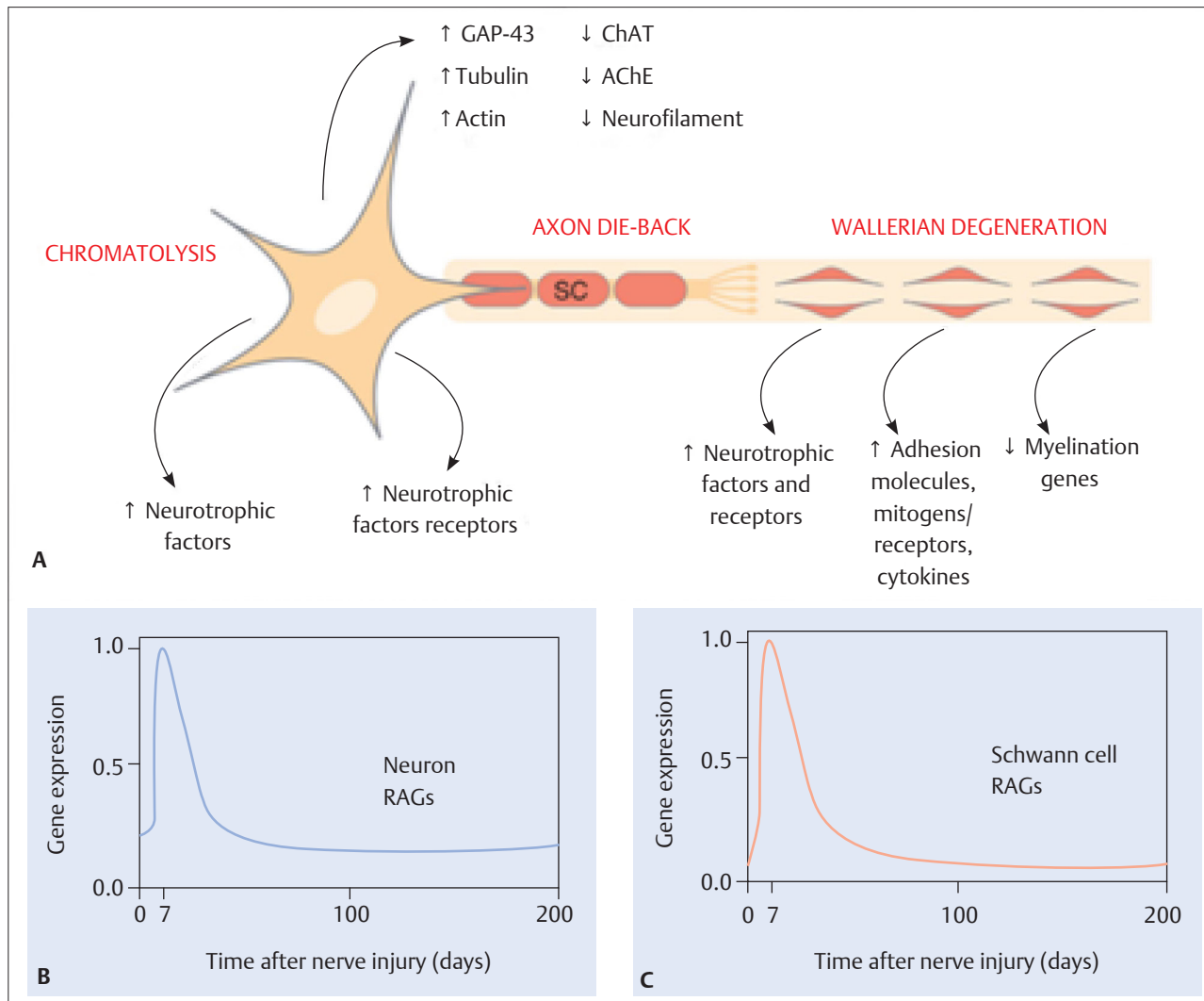


Fig. 2.4 Injury-induced molecular changes in injured neurons and proximal and distal nerve stumps. **(A)** After nerve injury that disrupts axons, the axotomized neuron undergoes the morphologic process of chromatolysis in which the nucleus moves to an eccentric position and upregulates regeneration-associated genes (RAGs), including GAP-43 and the cytoskeletal proteins tubulin and actin. The neuronal nucleus downregulates genes associated with neurotransmission in motoneurons, including choline acetyltransferase (ChAT) for the synthesis of acetylcholine (ACh) and acetylcholine esterase (AChE), which breaks down ACh. The neurofilament content that is associated with axon diameter declines concomitant with the decline in axon diameter proximal to the axon injury site. Distal to the injury, the axons separated from the cell body undergo Wallerian degeneration, and the Schwann cells that formerly myelinated the axons undergo cell division, downregulate genes associated with myelin, and express several molecules that support axon regeneration. The latter molecules include adhesion molecules and neurotrophic factors. Immediately after the distal nerve stumps are detached from the cell body by axon transection, a cell body reaction ensues that consists of expression of RAGs in the neurons, including GAP-43, tubulin, and actin **(B)**, and RAGs are also expressed in the denervated Schwann cells of the distal nerve stumps **(C)**. The RAGs expressed in Schwann cells include several neurotrophic factors and the p75 receptor. The increased expression is not sustained, however, and declines to low levels 1 to 4 weeks after the injury. The short-lived expression of RAGs accounts for the progressive decline in the maximum capacity of injured neurons to regenerate their axons and for the Schwann cells to support regenerating axons as the duration of nerve regeneration is prolonged by distance and/or time of regeneration.

Adapted from: Gordon T, Sulaiman W, Midha R. Pathophysiology of surgical nerve disorders (Peripheral Nerve Section Editors- A Filler, E Zager and D Kline). In: Youmans Textbook of Neurological Surgery, 6th Edition (R Winn, Editor), Elsevier, 2011.

anatomical correlates is essential for appropriate decision making, including indication for surgical intervention, timing and applicable approach, expected recovery, and prognostication. As previously discussed, timing of the intervention reflects directly on the expected return of function where in most cases early repair allows for a more favorable recovery, although timing of repair depends on the type of injury, wound condition, and vascular supply.⁹⁸ Some of the principals for surgical repair of nerve injury include tension-free repair, minimizing perineural tissue damage, and care for the neurovascular structures in order to reduce postoperative scar formation and fibrosis.

Hallmark of the surgical intervention for entrapment neuropathies is neurolysis (decompression of the neural tissue) procedures which can be either partial or circumferential. Chronic nerve compression creates a neural scar that alters neural blood flow and causes a form of chronic wound healing consisting of inflammation, cellular proliferation, angiogenesis, and connective tissue remodeling. Performing an early surgical decompression offers the optimal treatment option for patients with a nerve compression injury.^{46,99}

Following complete nerve transection, direct end-to-end coaptation is optimal management when the gap is minimal and the two stumps can be approximated with no tension and good fascicle alignment.^{100,101} The gold standard for nerve reconstruction in case of nerve gap, which cannot be approximated and coapted with no tension, is autologous nerve grafting. The harvested graft undergoes Wallerian degeneration¹⁰² and provides mechanical scaffold including SC basal lamina, neurotrophic factors, and adhesion molecules.^{87,103}

In cases of root avulsion (preganglionic injury) or injuries necessitating long nerve graft for reconstruction, nerve transfers (so-called neurotization) represent a practical surgical approach. Nerve transfers involve the repair of a distal denervated nerve element (recipient) by using an adjacent donor nerve by sacrificing a lesser needed muscle function to revive more desirable function. Reinnervating the recipient nerve close to the target muscle allows for short regenerative pathway and hence reduces axonal attrition by decreasing the effect of both chronic SCs denervation and chronic axotomy.^{32,37} Moreover, since the surgeon chooses the donor and recipient nerve, both of which

can be relatively “pure” motor or sensory fascicles, the influence of axonal misdirection on functional outcome can be partially mitigated.

Conclusion

Tremendous amount of progress has been made in our understanding of microanatomy, pathophysiology, and microsurgical management of injured nerves. These advancements, particularly the greater utilization of nerve transfers, have improved the quality of care provided to patients inflicted with nerve injuries and often result in better functional recovery. However, the other groups of patients that fail to recover good function despite excellent microsurgical care still pose a challenge to the nerve surgeon. The upregulation of RAGs is short-lived such that there seems to be a time window of opportunity during which SCs provide a growth-supportive environment and the injured neurons can regenerate their axons. This time-limited upregulation of RAGs and the slow rate of axonal regeneration result in progressive loss of neurotrophic support for the injured neurons and their regenerating axons and hence in chronic SC denervation and chronic neuronal axotomy.^{78,87,88} Therefore, two possible approaches to combat the gap between timing of upregulation of RAGs and slow rate of regeneration will be to (1) accelerate rate of axonal regeneration, and/or (2) sustain the neurotrophic environment for regenerating axons for longer periods. Brief (1 h) low-frequency electrical stimulation has been shown to accelerate axonal regeneration by modulating the expression of RAGs.^{29,104,105} Likewise, the beneficial effects of application of neurotrophins on axonal regeneration have been demonstrated experimentally, either exogenously^{91,106} or via the use of genetically engineered lentivirus which stimulate the production of neurotrophins.¹⁰⁷ Reactivation of chronically denervated SC by exposing them to cytokines such as transforming growth factor- β has been shown to promote nerve regeneration,¹⁰⁸ and transplantation of stem cells into the distal nerve stumps also show very promising results with regard to nerve regeneration.¹⁰⁹ Extensive research has also been done in the design of an enhanced nerve guidance channels or conduits that not only may eliminate the need for autografts but also

will allow for positive modulation of the growth-permissive environment for axons traversing the guidance channels into the distal nerve stumps.^{110,111} Perhaps, the ultimate solution to improve functional recovery in the subset of patients that currently do not do well with microsurgical repair is a combination of several neurobiological approaches to overcome the challenge of limited time window for optimal nerve regeneration.

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