Nerve Surgery: A Review and Insights about Its Future

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There have been considerable changes in the management of nerve injuries, entrapments and tumors in the past century, especially as they relate to neurobiology, pathophysiology, pathology, and surgical repair of these major neuropathies. This review revisits some of these major advances in the field of nerve injury and repair and provides some insight into the future of management of nerve pathology as seen by the authors. We apologize in advance for any omissions, as it is not our intent to ignore or de-emphasize advances in the field or those who have made them, but rather to provide a selective review.

HISTORICAL PERSPECTIVE

In the first half of the past century, the current knowledge in management of nerve injuries was formulated based of the results and experiences gained during World War II and previous wars. The outcomes of surgical treatments of war-related nerve injuries were less than optimal, especially those from nerve grafting. This discouraged many neurosurgeons from continuing in the field of nerve surgery, as well as the use of nerve grafting techniques. However, publications on surgical repair of injuries in civilian casualties from the second half of the past century and in recent years provided more encouraging results and are probably the impetus for some of the recent advances in the management of nerve pathology, including tumors and entrapments.

Nerve surgery is an exciting field as it affords the surgeon a broad playing field anatomically: one day, one is working in the buttock; the next day, in the neck; and yet another day, in the shoulder or the knee. In addition, few disciplines so thoroughly combine physiology with anatomy.

RECENT ADVANCES

In the past few decades, there has been a tremendous amount of research targeted at improving clinical outcomes in patients with nerve pathology, especially as they relate to clinical diagnosis and intra- and postoperative management of these disease entities. Many advances have been made in the area of neurobiology of nerve injury and regeneration and more attempts are being made in the area of translational research, especially with the usage of nerve conduits for nerve repairs in place of nerve grafts.

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CLINICAL DIAGNOSIS PERSPECTIVES

The importance of taking detailed but relevant history from patients and mastery of clinical examination skills cannot be overemphasized. These are the cornerstones of the surgical management of neuropathies. There is no substitution for a thorough examination of the limbs muscle by muscle. History taking and clinical examination are far more important than ancillary tests, such as electromyography (EMG) and imaging studies (*Table 5.1*).

The concept of "diagnosis of exclusion" is an essential part of the initial approach to diagnosis of nerve pathology. In general, most peripheral nerve diagnoses should only be entertained after the exclusion of other disorders. This is especially true for the diagnosis of Parsonage-Turner, Thoracic Outlet Syndrome (TOS), and entrapment syndromes. Always exclude trauma, tumors, and metabolic causes. Surgical consent and discussion need to be broad and should include the risks of 1) potential loss of some or more function, 2) minor and major complications involving adjacent structures such as vessels, lungs and peritoneal cavity contents, and 3) possibility of repair and reoperation.

INTRAOPERATIVE PERSPECTIVES

Microsurgery

As with any other neurosurgical operations, mastery of the required incisions, surgical approaches, and surgical anatomy is of utmost importance. There is little to no role for short incisions and small exposures. The nerve should be exposed proximal and distal to the lesion. Other nerves, nerve branches, and/or vessels should be dissected, identified and protected.

Since World War II, significant advancements have been made in the surgical repair of severed nerves, especially in the fields of microsurgical techniques for nerve repair, nerve grafting, and intraoperative neurophysiological evaluation of nerve lesions and regeneration.[9,16,28] The invention of the operating microscope and loupes, as well as the development of microinstruments, such as microdissectors, microscissors, and fine forceps, provide sufficient precision and enhance nerve repair a good deal. Another significant development has been bipolar

TABLE 5.1. Role of nerve conduction studies and imaging

With regards to EMG, the following should be emphasized:
- EMG should be more than just conduction studies and must include muscle sampling;
- Patients can have clinical muscle function despite deinnervational changes;
- Patients can have persistent paralysis despite nascents or reduction activity in denervational changes, such as fibrillation and denervation potentials;
- Muscles related to neighboring nerves or plexus elements can show persistent EMG changes despite good function;
- Conduction studies are not always useful especially for ulnar nerve and brachial plexus cases.

Imaging studies are important, but:
- MRI is most useful for tumors, occasionally it may also be useful for entrapments and injury;
- To date, in most institutions, MRI not a substitute for CT-myelogram, especially in investigating root avulsions
- Do not forget plain x-rays! May pick up parrot's beak, or the C7 spinous process or humeral condyle on plain x-rays.

coagulation, which permits hemostasis of bleeding points at the epineurial and interfascicular neural levels, with minimal associated damage to the nerve itself.

Although it is generally accepted that the clinical treatment of a severed nerve is microsurgical repair, the strategy adopted by surgeons for the more frequent lesions in continuity differ and the timing of nerve repair remains more controversial. However, our published experience shows that nerve repairs, or at least an exploration of the injured nerve, should be undertaken when a few months have elapsed and there is no electrophysiological (EMG/NCS) or clinical evidence of early functional recovery. For example, injuries to large nerve trunks, such as sciatic nerve or brachial plexus, should be explored after 3 to 4 months if no evidence of functional recovery.

If there is a sharp clean transection and exploration is within 72 hours, any distance between the two stumps caused by elastic retraction can be overcome and the ends reapposed. On the other hand, blunt transection is best repaired at 2 to 3 weeks, at which time the amount of stump resection to achieve healthy nerve tissue will be obvious. If there is a defect caused by loss of nerve tissue, the chance of success decreases in inverse proportion to the length of the defect, and a graft procedure in the form of a secondary repair is preferable. In cases in which the need for a grafting procedure is suspected, prepping of the patients should include body areas where nerve grafts may be harvested. Detailed illustrations of the techniques of peripheral nerve repair have been described previously and we refer the readers to the published manuscripts and textbooks.[16,31,40]

Intraoperative Nerve Action Potential (iNAP) Recording

The senior author (DGK) pioneered the application of iNAPs to the evaluation of the regenerative capacity of damaged nerve. This was essential as it prevents inadvertent resection of nerves that still have the potential for recovery and provides vital information about irreversibly damaged nerve segments and, thus, their need to be repaired. Before iNAP, the technique of evoked muscle contractions was popularized by Nulsen and Lewey[35] to determine whether or not there was evidence of regeneration. However, the problem with such technique included: 1) a solely axonotmetic nerve with an excellent potential for spontaneous recovery could demonstrate a nerve conduction block marked enough to prevent a muscle contraction, which, however, did not mean that all axons were dysfunctional; there were just not enough distal functional ones to elicit a visible muscle contraction; 2) after most nerve injuries, it takes many months for enough nerve fibers of sufficient size and myelination to reach muscles for stimulation alone to be possibly helpful; and 3) stimulation of nerve and recording from the muscle can only be useful in serious nerve injuries many months later, and then it may be too late for effective repair if such traces are flat or severely depressed.[28]

iNAP allows for early evaluation of nerve injuries and a determination of the extent of nerve damage. It can be applied 2 to 3 months after most focal injuries, and 3 to 4 months in less focal lesions caused by stretch/contusion or shotgun injuries. With its application, the nerve surgeon can sort out the management strategy for approximately 70% of nerve injuries in which nerve segments appear in continuity with a variable amount of swelling and/or epineurial scar and yet are nonfunctional (*Fig. 5.1*). Nerve action potential recordings can document the extent of a partial injury or prove that there is a neuropraxic block in the early days after the injury. When iNAP is applied months after injury, it can differentiate an axonotmetic (positive NAP across the lesion) from a neurotmetic injury (negative NAP across the lesion). These NAP studies help determine 1) when early surgery is or not indicated in lesion in continuity; 2) the proximal extent of healthy axons in injured nerves; 3) sites of entrapments; and 4) nerve fascicles entering and exiting the core of neural sheath tumors from those less involved and able to be spared.

Nerve Grafts

The clinical treatment of a severed peripheral nerve involves either surgical realignment of the injured nerve

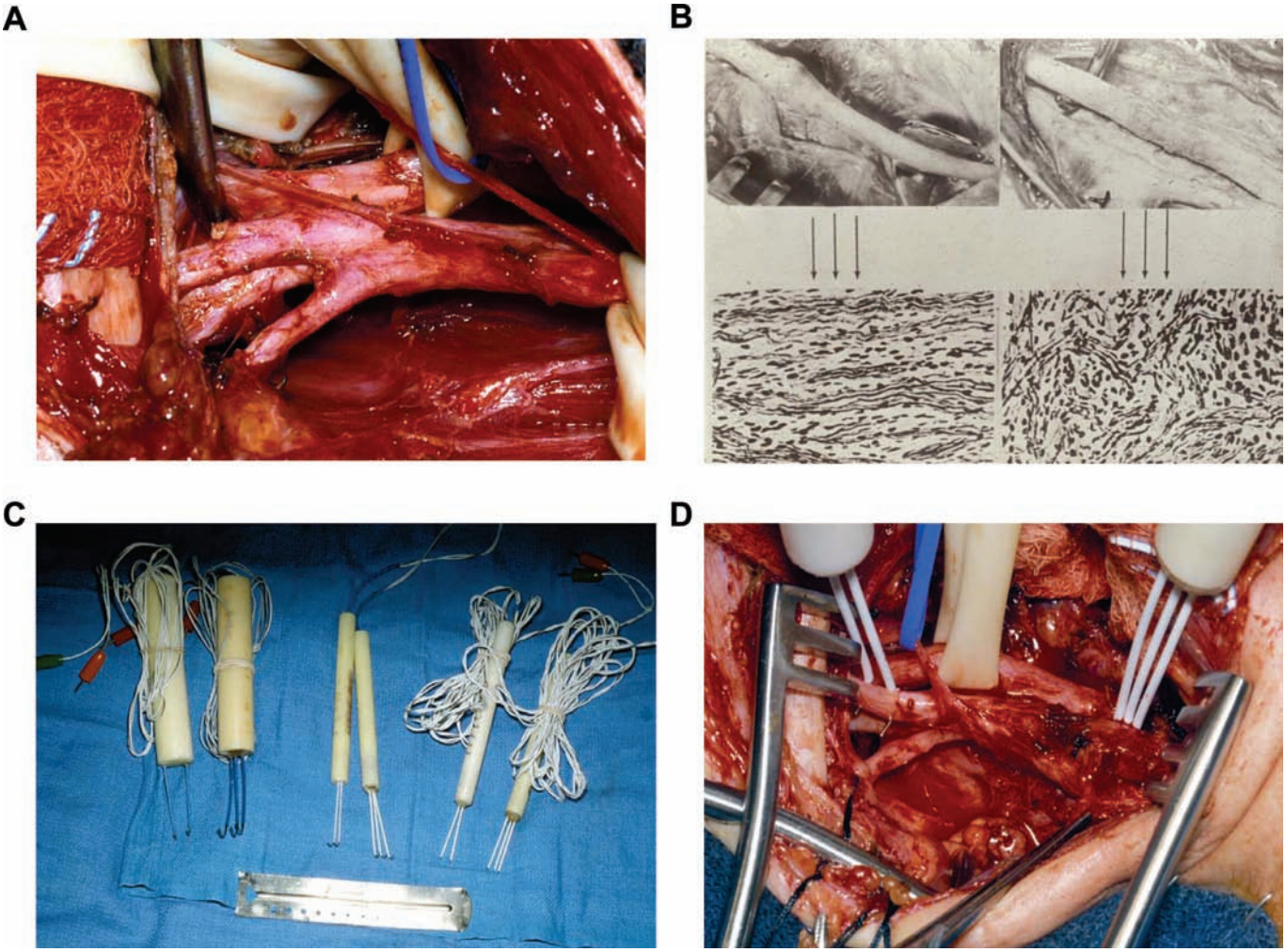

FIGURE 5.1. Intraoperative nerve action potential recordings are essential for intraoperative decision making. *A* and *B*, lesions-in-contituity, the extent of which cannot be discerned by gross inspection, as demonstrated by the histological preparations in *B*. *C*, recording electrodes used for nerve action potential recordings and their application intraoperatively (*D*).

stumps (i.e., primary neurorrhaphy) or the use of an autologous nerve graft to bridge a larger defect. The nerve grafting technique was first reported between the years 1870 and 1900, but it was Millesi[33] who wrote extensively on the subject of nerve grafting. His work demonstrated that nerve grafting without tension was superior to epineurial suture under tension and that tension at the repair site induces scar formation and, hence, nerve repair without tension is most desirable, because the more scar tissue present at the repair site, the less satisfactory functional recovery. Tension across a direct suture repair decreases blood flow and promote proliferation of connective tissue within the nerve, which may block effective axonal regeneration.[31,33] Acute, excessive stretch may cause intraneural hemorrhage, resulting in scar formation and axonoplasmic degeneration; subsequent maturation of scar tissue may shrink and constrict the nerve fibers and, may result in the formation of a neuroma in continuity.[31] However, whenever there is small to moderate gaps, it may be preferable to mobilize nerve ends to allow direct nerve repair (without tension) which results in better functional recovery than graft repair.[31,49]

Nerve grafting techniques include the use of either a free nerve graft or a vascularized nerve graft in the form of pedicle grafts or as a free vascularised graft transfer.[33] Nerve grafts can be classified according to their biological origin. Autografts are harvested from the same individual, allografts (or homografts) come from an individual of the same species, and xenografts (or heterografts) are from an individual of another species. Autografts, which are the "gold standard" for nerve grafting surgery, are harvested from the same patient and do not pose immunological problems. Nowadays, the donor nerves used for nerve grafting are commonly expend-

able sensory nerves that can be harvested without causing major problems, except for some loss of sensibility at the donor sites. Commonly used donor nerves include the sural nerve, lateral antebrachial cutaneous nerve, anterior division of the medial antebrachial cutaneous nerve, dorsal cutaneous branch of the ulnar nerve, and superficial sensory branch of the radial nerve. The choice of donor nerve to be used is dictated by the cross-sectional area of the nerve to be repaired, the length of the nerve gap, and the extent of donor site morbidity. The main donor nerve for free grafting is the sural nerve, which can be excised to a length of 30 cm or more and is easily assessible.[16,31,33]

The use of nerve grafts obtained from another human being is warranted in situations in which repair of large defects created by some brachial plexus or sciatic nerve injuries is limited by the inadequate number of available segments from autografts. However, because allografts trigger immunological response and there is a risk of rejection, the use of immunosuppressive treatment is required to prevent rejection. Hence, patients receiving this type of nerve grafts must be willing to accept the potentially dangerous side effects of the chemotherapeutic agents used. Xenografts are derived from animals of another species and they are also used in a similar situation as outlined above for allografts and require the use of immunosuppressive therapy. The use of xenografts is, thus far, limited to experimentations in animals.

Nerve Conduits

Donor site morbidity can be a nuisance in autologous nerve grafting, especially when additional and extensive surgery is required to harvest the grafts, and the use of allo- or xenografts is still mostly experimental for the reasons discussed above. In addition, functional recovery after both direct nerve repair and secondary repair with or without grafts is still suboptimal. Hence, there is the need for alternative strategies to optimize nerve regeneration and eliminate the use of nerve grafts and the adverse effects associated with their use.

Recent advances in the neurosciences, especially in the field of neurobiology of nerve growth and regeneration (in vivo and in vitro observations), genetic engineering and the development of novel biomaterials provide insights into the development of new therapeutic approaches to improve surgical treatment of peripheral nerve injuries. Natural or synthetic guidance channels are being developed as alternatives to autografts. Guidance channels help direct axonal sprouts from the proximal stump to the distal nerve stump. They also provide a conduit for diffusion of neurotropic and neurotrophic factors secreted by the Schwann cells (SC) of the injured distal nerve stump and minimize infiltration of fibrous tissue.[26] They may also be used as a means of delivery of molecules such as extracellular matrix molecules (e.g., laminin, fibronectin, and some forms of collagen) and growth factors (e.g., NGF, BDNF, IGF-1 and IGF-II, PDGF, bFGF and aFGF, CNTF) that have been shown to promote nerve regeneration.[20,26,48]

Recently, several synthetic nerve guide implants have been introduced and approved for clinical use to replace nerve autografts. Recent publications suggest that, for short (1–4 cm) nerve defects, resorbable implants provide promising results that are comparable to those obtained from autografts.[48] Likewise, no immunosuppression is required with the use of the implants. However, a number of late compression syndromes have been documented for non-resorbable implants and functional recovery is often poor when the implants are used to bridge larger nerve defects. Incorporation of various neurotrophic factors, growth-permissive cells such as SCs may sustain the growth-promoting function of the nerve implants while axons regenerate through them to innervate the distal nerve stumps.

Nerve Coaptation Alternatives

Nerve-to-nerve suture may induce fibroblastic proliferation and possibly cause significant scarring that may lead to compression and misdirection of regenerating axons. To avoid this unpleasant side effect of using suture material, alternatives to nerve sutures have been vigorously investigated. The use of laser to seal shut the epineurium was tested, but did not gain major popularity, partly because it provided inadequate tensile strength and many found that there was still a need for stay or holding sutures.

Narakas[34] summarized the indications for fibrin use in nerve repair in 1988. Since then, its use has steadily gained popularity in clinical practice in North America. There is experimental evidence for the various advantages of the use of fibrin glue. A recent study by Ornelas et al.[36] compared the use of fibrin glue and microsuture in the repair of rat median nerve and found that nerve repairs performed with fibrin sealants produced less inflammatory response and fibrosis, better axonal regeneration, and better fiber alignment than nerve repairs performed with microsuture. In addition, the fibrin sealant techniques were quicker and easier to use. The authors conclude that fibrin sealant represents a good alternative technique to microsuture for peripheral nerve repair. The use of fibrin sealant has also been reported in humans, especially in the repair of facial nerve in which very good results are obtained.[6] It is of utmost importance that proper alignment of the nerve segments be ensured before application of the fibrin glue to prevent misdirection of regenerating axons, especially when dealing with mixed nerves. One potential negative is that suture can be used to "fishmouth" or spread the ends of a graft when the lead out surface is greater than that of the graft. This cannot be done with the fibrin glue techniques without the addition of sutures.

End-to-side Repair

End-to-side neurorrhaphy was popularized by the experimental data of Viterbo et al.[47] in which they demonstrated that fibers can branch out of a relatively intact nerve when the distal nerve stump of another nerve is sutured to it end-to-side. The technique seems most successful when the epineurium is opened and there has been a small amount of damage to the enclosed fascicles during the placement of a distal nerve stump to the whole nerve. Whether sufficient axons regenerate into recipient distal nerve stumps to generate useful function remains to be clearly demonstrated in a well designed human study. Likewise, it is uncertain whether or not any significant measurable reduction of function occurs in the donor nerve. Primate studies at Louisiana State University Medical Center demonstrate that the number of axons branching into the recipient distal nerve stump is directly proportional to the extent of damage to the donor nerve and that there is some compromise of the function of the donor nerve. Therefore, one wonders whether or not it is not preferable to preferentially use functionally replaceable nerve branches to innervate the recipient distal nerve stump instead of the non-selective injury that accompanies the end-to-side repair.

A key question to answer as far as end-to-side repair is concerned is whether or not the axons growing into the recipient nerve represent axons that are lost by the donor nerve or indeed represent sprouting. Are these axons pruned from the donor nerve once they innervate the recipient nerve target organs? Preliminary experimental data from our laboratory (OARS) suggest that some of the axons in the recipient common peroneal nerve are as a result of sprouting from the donor tibial nerve. Using a backlabeling technique, we found that rat tibial motoneurons innervate both tibial innervated and common peroneal innervated muscles at the same time, as demonstrated by their double-labeling. The functional relevance of such motoneurons is questionable, as they innervate functionally antagonistic muscles. Therefore, perhaps the use of end-to-side repair should be limited to nerve repairs in which nerve transfers are deemed impossible (i.e., functionally replaceable branch of the donor nerve could not be obtained).

Spinal Cord Implantation

A potentially exciting area for further research is the reimplantation of avulsed nerve roots into the spinal cord or the use of implanted grafts to lead axons out of the spinal cord. To date, as with many of the end-to-side models, the outflow of axons has been less than robust and the restoration of clinically useful function is small, but perhaps further refinement will bring better results.

Nerve Transfers

The technique of nerve transfers aims to neurotize denervated distal nerve stumps and their target organs with regenerating axons of freshly cut foreign and often nearby proximal nerve stumps.[32] It is a technique that is quickly evolving and has been extensively discussed. The overriding principles include 1) minimizing the distance over which borrowed axons travel to reinnervate the denervated targets by suturing the borrowed proximal nerve stump to the denervated distal nerve stump as proximal to the target organ as possible and avoiding the use of nerve grafts whenever possible and 2) using functionally compatible motoneuronal pool (i.e., donor motoneurons are agonists as they relate to the recipient targets). Although, the full spectrum of cortical plasticity to nerve transfers is not worked out, there is evidence that cortical plasticity plays a major role in the functional recovery obtainable after nerve transfers.[30]

Nerve transfer techniques include intraplexal transfers, such as medial pectoral-to-musculocutaneous and ulnar-to-musculocutaneous, and extraplexal transfers, such as intercostals-to-musculocutaneous. The types of nerve repairs and/or nerve transfers performed are dictated by the nature of the injury to the brachial plexus.[27] Of course, all acute clean laceration need urgent direct repair. Our preferences for more complex plexus injuries are outlined *Table 5.2, A* and *B*.

The emerging controversy concerns whether or not reconstruction of complex brachial plexus injuries should include an exploration of the supra- and infraclavicular plexus with the intention of finding good fascicular structures for lead outs to division or cords or graft repairs? Based on our published experience of outcomes of surgery for gunshot and stretch injuries to the brachial plexus in which approximately 70 and 54% of patients recover to Grade 3 or higher (LSU grading system) after surgical repair, respectively, we think that an exploration of the brachial plexus is a vital part of the surgical management of these complex injuries. Having said that, the results of nerve transfers are good so they can almost always be added in.

Nerve Tumors

The era of nerve sheath tumors, especially neurofibromas, being inoperable is history. Nowadays, most benign neural sheath tumors can be safely excised with minimal or no neurological sequelae. However, a thorough understanding of the surgical principles, approaches, and techniques involved with removing nerve tumors is essential.[15,32,46] Surgical principles for nerve sheath tumors focus on surgical decision making common to all peripheral nerve sheath tumor operations and then on that particular to a given tumor type. Hence, the treatment of solitary nerve sheath tumors, either schwannoma or neurofibroma, is different from that of multiple nerve sheath tumors and plexiform tumors of von Recklinghausen's disease (VRD), which is again different from the treatment of malignant nerve sheath tumors. Each of these groups requires different rules for decision making.

We perform all surgical cases under general anesthesia, but ensure that the patients are asleep (but not paralyzed) as

TABLE 5.2. Repair preferences

Repair preferences for C5/C6 stretch or C5/C6/C7 stretch injuries
1) Neurolysis if NAPs indicate regeneration
2) Direct repair if NAPs are negative (flat) and proximal fascicular structure is found on sectioning spinal nerve plus addition of medial pectoral to split musculocutaneous nerve (for C6 avulsion) or accessory to suprascapular nerve (for C5 avulsion)
3) Accessory and medial pectoral transfers and, less frequently, descending cervical plexus transfers if NAP studies indicate preganglionic lesion or sectioning indicates pre- and postganglionic lesions of C5 and C6.
4) An alternative to use of medial pectoral branches to innervate musculocutaneous nerve is the Oberlin transfer where ulnar motor fascicles are sutured directly to the motor branch of the musculocutaneous nerve
Repair preferences for C5 through T1 stretch injuries or flail arm
1) Neurolysis where NAPs indicate regeneration. (This finding is infrequent but does occur)
2) Direct repair if NAPs are negative and yet, on sectioning, fascicular structure is found proximally. Grafts are from proximal spinal nerves to divisions or cords. Added in are the following: a) accessory to suprascapular nerve; b)descending cervical plexus to posterior division of upper trunk or middle trunk and its divisions; c) intercostals (3 or 4) to a longitudinally split portion of musculocutaneous nerve.
3) If all five plexus roots are avulsed, the following repairs are preferred: a) accessory nerve to suprascapular, b) intercostal nerves to musculocutaneous nerve, and c) either descending cervical plexus or accessory nerve input to sternocleidomastoid muscle placed to posterior division of upper trunk.

the use of disposable nerve stimulator, as well as INAPs constitute an essential part of safe and gross total resection of the tumors. The surgeon must ensure complete exposure and identification of all relevant anatomic structures around the tumor, adequate 360-degree tumor exposure and fascicular dissection at the poles of the tumor to spare all but the fascicles entering and exiting the tumor mass. With this approach, loss of function is minimal in those patients with no preoperative deficits, with 91% with schwannomas removed demonstrating no loss of function and the remaining 9% showing 3/5 or 4/5 weakness after surgery. These results were slightly worse for solitary neurofibromas, with 78% of patients demonstrating no loss of motor function and 22% demonstrating slight motor deficits after surgery.

Needle biopsy or partial open biopsy has a limited role in the diagnosis of nerve sheath tumors. Its ability to establish the correct diagnosis is still questionable, due to either small sample size, sampling error, or the misinterpretation of histological specimen (even in experienced hands due to similarity among the different tumors). Of great importance is the rather frequent biopsy-related injuries to tumor-related nerve fascicles leading to new neurological deficit. Incomplete tumor removal generally adds nothing to the care of the patient. The complications and morbidity of surgery significantly increase once virgin surgical planes have been violated. If a neural tumor is exposed without the skill or ability to achieve its removal, the incision should be closed and a second operation planned when such technical expertise is available.

The multiple neurofibromas of VRD cannot be cured by surgical resection, even though individual ones can often be excised with minimal deficit. The presence of a tumor by itself is not an indication for surgical removal. Rather, it is the presence, alone or in conjunction with pain, neurological deficit, and large size exerting significant mass effect on nearby structures. In the case of plexiform neurofibroma in which there is no intervening neural tissue, the usual reason for operation is persistent pain not responding to medical treatment. Intraoperative evidence of malignancy, such as poorly-defined capsule, infiltration of nearby structures warrants a frozen section, which may help in the confirmation of malignancy. If malignancy is highly suggested by the frozen section, gross total resection of the tumor along with clearly involved fascicles as well as a segment of the proximal and distal nerve is indicated. Further surgical and adjuvant treatment options are discussed with patients once a final pathology report is obtained.

Complications and their Avoidance

Complications can and do occur and can be serious and life-altering. They can occur at different stages of patient care starting from preoperative work-up, diagnosis, surgical decision making, operative techniques, and postoperative care. Mastery of history taking, physical examination, and judicious use of ancillary tests to arrive at a correct diagnosis form the basal knowledge that every nerve surgeon must be conversant with. Misdiagnosis leads to mismanagement.

Surgical decision making is a dynamic process that begins in the preoperative period and ends at a patient's discharge from the hospital. Sometimes, total excision of a nerve tumor may cure the tumor, but hurt the patient. It is advisable to involve surgical colleagues, such as vascular,

general, cardiovascular, and orthopedic surgeons, whenever indicated to assist in the anatomic exposure of the pathology. Be aware that atlases and books show the normal anatomy and where to go, but not necessarily what to expect during the actual operations. Participation in either practical clinics and/or being involved in actual surgical cases are important ways to significantly improve the technical know-how of the nerve surgeon. Nerve surgery can be very difficult, stressful, and lengthy. It is advisable not to plan to do too much in one day and to avoid lengthy and difficult cases when tired.

Operative notes need a description of actual findings and what was done and should not be left to assumptions by words such as neurolysis, repair, grafts, etc. Postoperative discussions may, and often do, include drawings and a realistic evaluation of outcome. Nerve repairs, especially those done with grafts take much more than 1 inch per month. The process of functional recovery is a lengthy one that takes 5 to 6 years. Not all repairs in all people or in all nerves work. Postoperative care demands a team approach.

POSTOPERATIVE PERSPECTIVES

Patient Follow-up Visits

Follow-up may be necessary by other specialists involved as well as by the neurosurgeon. Timing of follow-up visits varies depending on the initial outcome, length of time predicted for useful regeneration, and need for PT/OT and secondary procedures. The tensile strength of neural repairs is maximal at 3 weeks, so active PT/OT can usually begin after that. On the other hand, if the initial regenerative input is a year away, saving some PT/OT may be necessary depending on insurance coverage.

Outcomes Assessments

It is of the utmost importance that a universally acceptable numerical grading system for nerve pathologies and outcomes be developed to elevate the field to the scientific level it deserves and to assist us in the development of management strategies based on reliable data. The most popular grading scale is the Medical Research Council grading system. But, this system has shortcomings, some of which have been addressed in the more recent American systems, such as that from Louisiana State University Medical Center grading systems. New generation grading systems, which may be born out of a combination of the above-mentioned systems must further reflect the lifestyle or practical use of the limb that injury and/or its recovery permits.

Published studies on nerve injuries and repairs from both the war era and civilian experience are invaluable to the field with regards to obtainable treatment goals. With the availability of more sophisticated data gathering and analysis software, it is a lot easier to carry out outcome research in either war or peace. Given the tremendous advancements in the field of nerve regeneration strategies, nerve conduits and pain management, analysis of outcomes has never been more important than now.

ADVANCES IN NEUROBIOLOGY OF NERVE INJURY AND REGENERATION

Mammalian central nervous system (CNS) neurons are virtually incapable of regenerating axons after injury in contrast to their peripheral nervous system (PNS) counterparts, which do regenerate, albeit slowly and incompletely.[14] The myelinating glial cell of the PNS is the SC, which, in contrast to the oligodendrocyte in the CNS, provides a growth-permissive environment for axonal regeneration in both the PNS and the CNS, particularly in association with phagocytic macrophages, which infiltrate denervated distal nerve stumps to phagocytose the myelin of denervated SCs.[12,13,38] However, despite the capacity for axonal growth in the PNS and the permissive environment provided by the SCs of the distal stumps of injured peripheral nerves, functional recovery is often disappointing after PNS injury, even with microsurgical repair. To attain any form of functional recovery after peripheral nerve injury, axotomised neurons must 1) regrow the damaged axon, 2) upregulate and maintain the upregulation of the required regeneration associated genes (RAGs, e.g., GAP-43, tubulin, actin), and transcription factors such as c-fos, c-jun and KROX 24, all of which have been associated with axonal regeneration, 3) continue axonal regrowth through the lesion site (i.e., overcome inflammation-induced scar at the lesion site), 4) elongate the axons in the correct direction (correct endoneurial tubes), 5) topographically reinnervate their original target (target reinnervation), and 6) restore normal electrophysiological properties.[20,24] Successful completion of all these steps in the process of nerve regeneration require a well-coordinated and time-related change in gene expression of the injured neurons, the SCs of the distal nerve stumps, and the denervated muscles. Inadequacies in any of the steps of the regenerative process may lead to poor functional recovery.

Both CNS and PNS neurons can initiate the initial process of axonal regrowth by sending out axonal sprouts from the proximal stump of injured nerves, but only the PNS neurons can accomplish the other steps in the regenerative process as CNS neurons either fail to upregulate RAGs or do so at very low levels and, CNS initial effort to regrow axons aborts within the inhibitory environment of the denervated oligodendrocytes in the scar tissue.[8] Despite the seemingly excellent regenerative capacity of the PNS, clinical experience has established that functional recovery is often poor, particularly for injuries that sever large nerves such as brachial and lumbar plexus nerve trunks.[1,28,44] This is because the slow rate of regeneration (1–3mm/day) of injured neurons results in their progressive loss of RAGs expression (i.e., chronic axotomy) coupled with deterioration of the growth-

permissive environment provided by the SCs of the distal nerve stumps (i.e., chronic denervation). Another important factor that may further exacerbate the limited functional recovery after nerve injuries is the misdirection of many regenerating axons into the wrong endoneurial tubes and their reinnervation of inappropriate targets.[20,44] Internal endoneural fibrosis, both at the site of suture and along the length of the distal nerve stumps, as well as extraneural fibrosis and wound bed adhesions, may further hamper the regenerative process. These fibrotic changes are probably related to differential responses of different elements of peripheral nerve to mechanical loading. The endoneurial fibrosis may compromise clinical outcome whereas the extraneurial fibrosis and adhesions may impair local sliding of the injured nerve with limb movement, thereby putting the repaired nerve under undue tension and potentially compromise its microvascular bed.

The detrimental effects of chronic axotomy and chronic denervation of on nerve regeneration strongly suggest that there is a time window during which the regenerative milieu is optimal and, if axonal regeneration does not occur during this time, poor functional recovery ensues (*Fig. 5.2*)[4,18,19,23,42] The significance of active cell-molecular interactions between SCs and infiltrated macrophages is supported by the evidence that SC migration and proliferation, as well as axonal regeneration, are severely retarded in the C57Bl/Ola mouse mutant in which macrophage invasion is sluggish and Wallerian degeneration is delayed.[3,7,12] Macrophage phagocytosis of myelin and axonal debris from Wallerian degeneration eliminates myelin-derived growth inhibitors such as NI-35, NI-250, Nogo-A and MAG, thereby promoting axonal growth.[8]

Conversion of SCs from a myelinating phenotype to a non-myelinating phenotype after nerve injury is associated with their proliferation and their expression of growth factors, such as nerve growth factor, brain-derived neurotrophic factor, neurotrophin-4/5 and glial-derived neurotrophic factor, all of which have been associated with neuronal survival and axonal growth.[20,24,25] During regeneration of motor and sensory axons in vivo, a second phase of SC proliferation ensues,[37] a process mediated via the interactions between neuronally-derived neuregulin and erbB2, erbB3 and, to a much lesser extent, erbB4 receptors expressed by SCs.[10,11,29] Neuregulin induces the phosphorylation of erbB2 and erbB3 receptors and a subsequent formation of erbB2:erbB3 heterodimers, which, in turn, mediates SC proliferation.[10] When axonal regeneration is delayed, as is the case with chronic denervation and axotomy, SC proliferation is not maintained, their numbers decrease progressively, and their basement membranes and, hence, the endoneurial tubes fragment and disappear.[22,25,42,45] In addition, delayed reinnervation of distal nerve stump failed to reinduce the expression of GDNF compared to robust expression of GDNF after immediate suture.[25]

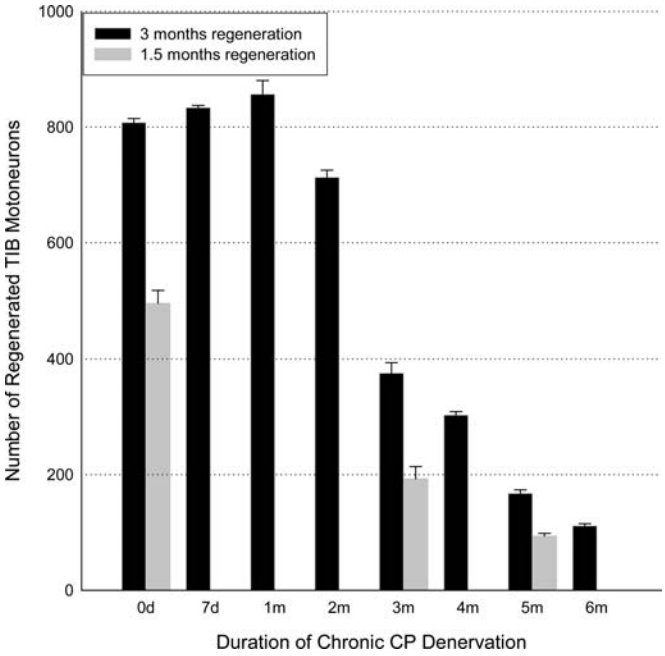

FIGURE 5.2. In a rat model of nerve injury and repair, freshly cut Tibial (TIB) nerve was cross-sutured into common peroneal (CP) either immediately (0 d) or after a delay of 7days to 6 months (i.e., variable duration of chronic CP denervation). Regeneration of TIB motoneurons into the CP nerve was allowed for either 1.5 or 3 months and the number of TIB motoneurons that regenerated into the CP nerve was assessed using retrograde labeling. The number of regenerated TIB motoneurons declined as a function of duration of chronic CP denervation, especially after a 4-week delay.

The progressive reduction in numbers of these long-term denervated SCs correlates with the progressive decline in expression of erb B2, erb B4 after 4 weeks[29] and a later decline (after 8 wk) of p75 receptors in denervated SCs.[50] In contrast to erbB receptors which mediate SC proliferation, p75 has been implicated in mediating their apoptosis.[17,39] Therefore, the earlier loss of expression erbB2 and erbB4 as compared with p75 suggests that there is a 4-week period during which apoptotic signals via p75 predominate in SCs leading to their death and subsequent reduction in their number. Interestingly, in animal experimentation, the period between 4 and 8 weeks coincides with the time during which the number of motoneurons which had regenerated axons began to decline (*Fig. 5.2*). Therefore, the temporal decline in the expression of erbB and p75 receptors, fragmentation and collagenization of the endoneurial tubes, as well as down-regulation of neurotrophic factors,[20,25,42,45] could explain, at least in part, the reduced axonal regeneration after delayed repair.

ASPECTS TO BE ADDRESSED

Microsurgery of injured nerves has improved so tremendously since World War II that one wonders whether any further technical advances will add to the degree of functional outcome obtained in patients. Multiple therapeutic targets have been identified from animal experimentation, which may improve functional outcomes. These include prevention of chronic axotomy via application of growth factors[5] and optimizing regeneration during the limited time window by accelerating regeneration using either growth-promoting molecules (e.g., FK506[43]) or electrical stimulation.[2] Sustenance of the growth-permissive environment of SCs is essential and experiments using transforming growth factor to reactivate chronically denervated SCs and incorporation of stem cells in the distal nerve stumps have been shown to have positive effects on nerve regeneration.[41] Ultimately, improving functional recovery after injuries to large nerve trunks will require using a combination of regeneration-promoting strategies.

Further studies are needed in the area of response of various nerve components to mechanical load with the objective to further elucidate the mechanism of scar formation in injured nerves. Indeed, there is a necessity to maintain some connective tissue framework as a scaffold for regenerating axons. On the other hand, factors leading to overproduction of collagen and, thus, scar need more intense study. The intraneural fibroblast seems to have its own behavioral characteristics which differ from fibroblasts elsewhere in the body.[21]

Clinical studies investigating potential "molecular markers" that may help to distinguish patients who are "good regenerators" from "poor regenerations" may shed more lights on the factors that are responsible for such variability in functional outcomes in patients.

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