

## TECHNIQUES OF PERIPHERAL NERVE REPAIR

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### ABSTRACT

Nerve injuries extend from simple nerve compression lesions to complete nerve injuries and severe lacerations of the nerve trunks. A specific problem is brachial plexus injuries where nerve roots can be ruptured, or even avulsed from the spinal cord, by traction. An early and correct diagnosis of a nerve injury is important. A thorough knowledge of the anatomy of the peripheral nerve trunk as well as of basic neurobiological alterations in neurons and Schwann cells induced by the injury are crucial for the surgeon in making adequate decisions on how to repair and reconstruct nerves. The technique of peripheral nerve repair includes four important steps (preparation of nerve end, approximation, coaptation and maintenance). Nerves are usually repaired primarily with sutures applied in the different tissue components, but various tubes are available. Nerve grafts and nerve transfers are alternatives when the injury induces a nerve defect. Timing of nerve repair is essential. An early repair is preferable since it is advantageous for neurobiological reasons. Postoperative rehabilitation, utilising the patients' own coping strategies, with evaluation of outcome are additional important steps in treatment of peripheral nerve injuries. In the rehabilitation phase adequate handling of pain, allodynia and cold intolerance are emphasised.

Key words: Nerve injury; nerve repair; nerve reconstruction; neuron; Schwann cell; nerve grafts; nerve transfer

### INTRODUCTION

Peripheral nerve trunks are very delicate structures consisting not only of the extended processes from the nerve cell body of the neuron – axons – but also of a large number of other cell components and intraneural blood vessels that react to trauma. The outcome of a nerve injury may be variable depending on the etiology of the trauma. Although nerve injuries range from nerve compression lesions, like carpal tunnel syndrome, up to severe rupture and avulsion of spinal nerve roots in brachial plexus lesions, the

focus on the present article is the handling of transection and laceration injuries of peripheral nerve trunks.

In clinical practise only around 3% of hand injuries include injury to peripheral nerve trunks. Even a minor injury to a finger causing a digital nerve injury (incidence 6.2/100 000 inhabitants/year) may induce dysfunction of the hand. The consequences of a median or ulnar nerve injury in the forearm are even more wide-ranging for the patient. The injury does not only cause problems in the patient's professional life but leisure activities are also severely impaired. Although costs of nerve injuries burden the health care sector, the main part of the total cost is caused by loss of productivity (sick leave) (1). The reason is that a large number of the patients with nerve injuries is in productive age (1). The costs to society for a median nerve injury in the forearm may exceed 50000 euros. An adequate and properly timed treatment of peripheral nerve injuries is crucial to achieve

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a reasonable satisfying clinical outcome although a complete nerve injury always will lead to permanent dysfunction in adults.

#### ALTERATIONS INDUCED BY A NERVE INJURY – NEUROBIOLOGICAL ASPECTS

The neurobiological alterations in neurons and Schwann cells are important to trigger the peripheral nervous systems into a regenerative state. After transection of a nerve trunk calcium-dependent proteases are activated in the axon distal to the site of lesion. Thereby, the distal part of the axon disintegrates and Schwann cells rapidly loose their myelin sheath that surrounds the axon. Macrophages invade the distal nerve segment to remove the myelin and the disintegrated remaining parts of the axon. Schwann cells react extremely rapidly to nerve injury with expression of crucial regeneration-associated factors (2, 3). Some Schwann cells even die after the injury. The large variety of factors that put the neuron and Schwann cells into a regenerative state or into programmed cell death (apoptosis) are controlled by specific intracellular signal pathways which are initiated after injury. There are several pathways of this so called signal transduction that includes activation of receptors and a number of events in the cell which leads to changes in the genes with the purpose to transform the cells to a regenerative condition. The different signal transduction pathways are activated, usually by phosphorylation of the subsequent step, in the cells. In Schwann cells, extracellular-signal-regulated kinase-1/2 (Erk 1/2) is rapidly phosphorylated close to the site of transection; a process which is required for proliferation of the Schwann cells (2). Another important factor is the activating transcription factor 3 (4). It was recently reported that ATF3, which is expressed in Schwann cells within a couple of days after injury, may be important for outgrowth of axons after a nerve injury (5, 6). The number of ATF3 expressing Schwann cells correlate to the length of axonal outgrowth and axons grow close to ATF3 expressing Schwann cells (6). Schwann cells proliferate in the distal nerve segment as a response to nerve injury. By proliferation and migration they can extend over a minor nerve defect if a fibrin matrix is present. Interestingly, Schwann cells loose their ability over time to produce factors that are necessary for axonal outgrowth (7–11). If there is a prolonged denervation of the distal nerve segment the Schwann cells turn unresponsive to outgrowing axons. In chronically denervated nerve ends Schwann cells down-regulate expression of c-erbB receptors (12), glial cell-line derived neurotrophic factor (GDNF) (11) and ATF 3 (7).

The neuron and the proximal nerve end, which contains axons, react to the transection trauma with similar transduction pathways as seen in the Schwann cells. The Schwann cells, close to the site of transection, go through the same type of changes as the Schwann cells in the distal nerve segment. More importantly, transection of the axon induces signals that are transferred up to the nerve cell body within sec-

onds to minutes (first phase) as well as hours, days or weeks after the injury. The intracellular transport system – axonal transport – transfers information from the site of injury by retrograde transport. Retrograde transported signals include factors that are either formed in the axoplasm at the site of injury or released from cells in the environment and taken up at the site of injury. Thus, a “positive” signal is transferred to the nerve cell body. The positive signals in the axon may consist of activated or conformationally modified substances that are connected to specific nuclear localisation signals, which are crucial for the convey via retrograde transport (13, 14). Attached to the complex of factors and nuclear localisation signals that is transferred by retrograde transport are importins necessary to transfer important proteins through the nuclear pores (15). These are very well controlled mechanisms in the neurons to regulate retrograde injury signalling in peripheral nerves (16). Examples of retrograde injury signals that are activated and necessary for transcription in the nucleus are Erk 1/2, JNK, ATF3 and STAT3 (3, 13). These signals are only part of the very complex mechanisms that are activated in neurons as a stress response to initiate regeneration. The signal transduction pathways are still incompletely understood and are focus of intense research. The “negative signal” is the loss of information normally transported with retrograde transport which further contributes to intraneural signalling after nerve injury. These positive and negative signals (second phase) reach the cell body within hours to days while a third phase is characterised by other positive signals originating from the surroundings of the formed growth cone or by signals that are released by cells at the site of lesion. The signals initiate gene expression in the nucleus of the cell. Such expression occurs early in neurons but the specific functions of all genes are still unknown.

In the final phase, as a response to a transection injury, there are probably signals from the outgrowing axons, particularly when the target is reinnervated. These signals imply that the direct outgrowth of axons should be finalized. Interestingly, some of the induced alterations, such as the transcription factor ATF3, are spontaneously down-regulated in neurons, not only in Schwann cells, over time. This may be one factor behind impaired regeneration when there is a delayed nerve repair (6, 7).

Reactions of the Schwann cells and the intracellular changes in neurons, particularly in the growth cone, are factors behind the conditioning lesion effect; an axonal injury made prior to a second test lesion leads to enhanced axonal outgrowth (17, 18).

Programmed cell death is triggered by proapoptotic molecules, which are released from mitochondria or through cell surface death receptors. Fascinatingly, there is a different reaction of motor and sensory neurons after an injury not only with respect to regeneration-associated factors (6, 7) but also regarding apoptosis. Sensory neurons show a more extensive cell death than motor neurons after injury over time (up to 40% of sensory neurons in dorsal root ganglia may die) if a nerve injury is not repaired. However, cell death of both types of neurons can be

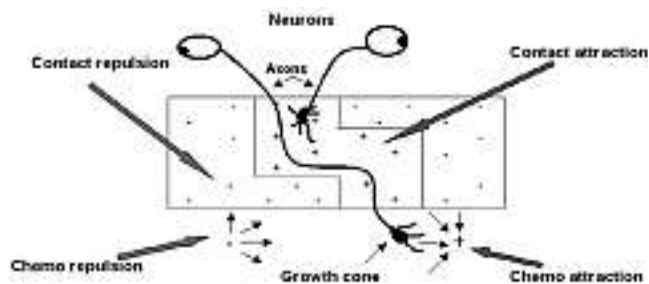


Fig. 1. The principal mechanisms by which axonal growth are directed. The tip of the sprouts from the transected axon – the growth cone – is influenced by attractive and repulsive mechanisms. The figure is reproduced by kind permission of Journal of American Society for Surgery of the Hand.

diminished if a nerve repair is performed early (19). Apoptosis is an event initiated very early and the pharmacological possibilities to reduce apoptosis have to be commenced within 24 hours after injury. An example of pharmacological substances that have been shown to diminish sensory cell death after injury is N-acetyl-cysteine (20–22). Thus, early nerve repair and pharmacological intervention decrease neuronal cell death.

When a nerve trunk is injured and the transected nerve ends are attached by surgery, axons grow from the proximal nerve segment into the distal nerve segment. The outgrowth is a very delicate process in which a large number of signals in the signal transduction mechanisms integrate at the growth cone where actin is polymerised and microtubules are re-assembled. In these processes which interact with the extracellular matrix and particularly integrins are important in this context (3). At the end of the transected axon a large number of sprouts are formed at the tips of which afore mentioned growth cone is formed. The growth cones have finger-like processes (filopodia) that palpate the environment with the purpose to find the best growth direction. If there are positive guidance cues the growth cone and sprouts are routed into that direction (attraction), while negative guidance cues lead to collapse of the filopodia (repulsion) forcing the growth cone to follow another path. The principal mechanism by which axons direct their growth is depicted in Fig. 1 (3).

In the gap between the proximal and distal nerve segment an inflammatory response occur and a fibrin matrix, filled with e.g. macrophages, is formed. Schwann cells can migrate from both ends where the migration of such cells takes part in concert with the outgrowing axons (23). An interesting question is how a new nerve trunk is created in the small gap between the nerve segments along with formation of the perineurium (24).

## THE TECHNIQUE OF NERVE REPAIR

A primary nerve repair is the preferred method after a nerve transection (25). It is done immediately after an injury or within two days. It is important that the

repair is done in a tidy wound. The procedure of repairing a nerve trunk can be divided into four steps. Initially the nerve ends are prepared to get a viable nerve end without necrotic tissue (preparation). The nerve ends are handled with care using microsurgical instruments. A pair of sharp micro scissors or a surgical blade can be used to remove the necrotic part of the nerve ends. The extent of resection can be difficult to judge if there is a laceration or a contusion by for example a gun shot. After the nerve ends are prepared, they should be approximated keeping in mind the importance of adjusting the length of the gap and the tension of the nerve segments (approximation). During the approximation the nerve ends can be slightly mobilised by dissection but one should avoid extensive intrafascicular dissection. The nerve ends are coaptated. It may be advisable to leave a minimal gap between the nerve ends. Such a gap is rapidly filled with a blood clot and a fibrin matrix is formed containing for example macrophages as pointed out above. In such a fibrin matrix Schwann cells migrate from both the proximal and distal nerve segment. The axons from the proximal nerve end grow in concert with the Schwann cells (23). The nerve repair is maintained by stitches (maintenance); 9–0 or 10–0 nylon (sometimes thicker suture materials can be suitable in specific cases) is inserted into the epineurium. Thus, interrupted epineurial sutures maintain the repair. In a digital nerve it may be enough with three 9–0 sutures, while in a larger ulnar or median nerve several interrupted sutures are applied, sometimes with thicker suture material (Fig. 2). When the sutures are placed one should try to avoid malrotation of the nerve ends. Identification of the longitudinal intraneural blood vessels may help in this.

In specific cases it is possible to identify individual fascicular groups for attachment (group fascicular nerve repair) (25), predominantly at a distal level where fascicles with specific targets are well defined. The ulnar nerve at wrist level is one nerve where such a repair technique can be used since it contains two separate motor and sensory components. All nerve repairs are performed by the use of surgical loupes (magnification  $\times 3.5$ ), but a microscope may in some circumstances be advisable.

## TUBES FOR NERVE REPAIR

Tubes to repair nerve trunks have been used experimentally to study the regeneration process. Silicone tubes were used in a clinical prospective study comparing tube repair with microsurgical nerve repair in median and ulnar nerve injuries (26). In principle there were no significant differences between the two methods 5 years after the repair except less cold intolerance after tube repair. The technique of tube repair is simple. The question of tissue reaction (27) has been focus for intense discussion leading to development of new biodegradable tube materials. A variety of tubes are available at the market for use in humans. However, few randomized clinical studies are available (28). In the future, tubes may be filled with supporting cells; a simple technique was recently pre-



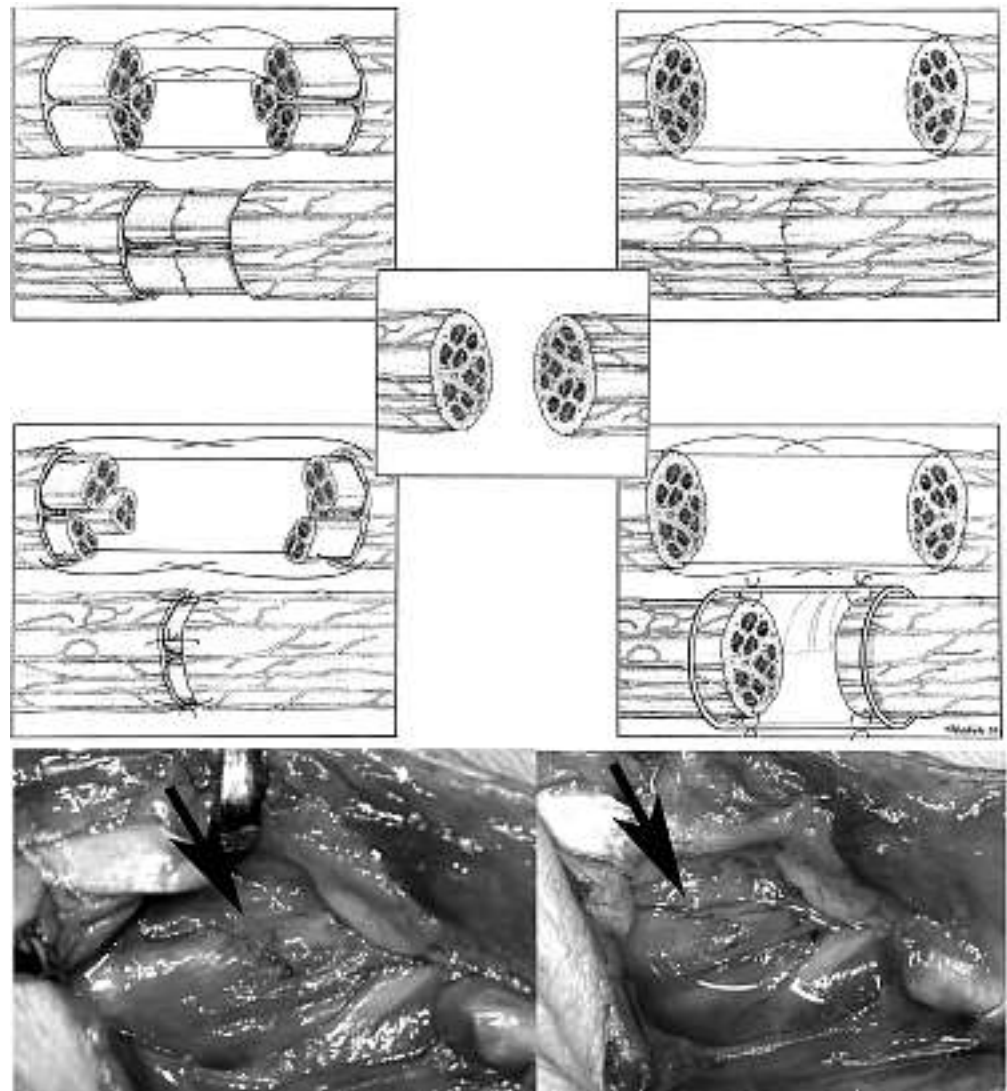


Fig 2. Four different techniques to repair a nerve injury; group fascicular suture (upper left); epineurial suture (upper right); combined epineurial and perineurial repair (lower left) and tubular repair (lower right). The photos show a transected median nerve just proximal to the wrist (arrow; left panel). The nerve was repaired by epineurial sutures (arrow; right panel). The figures are reproduced by kind permission of Neurosurgery Clinics of North America, Journal of Hand Surgery (Am) and Elsevier.

sented where Schwann cells can be harvested from the injured nerve segments and applied to a tube (29).

#### TIMING OF NERVE REPAIR

Timing of nerve repair, as outlined in the paragraphs describing neurobiological events in Schwann cells and neurons, is an interesting issue. For several reasons a primary peripheral nerve repair is favourable. Technically, a primary repair of a sharp injury is easier. The rotation of the nerve segment can be easily judged since the epineurial blood vessels can be identified on the surface of the nerve trunk. The nerve stumps can also easily be cleaned, i.e. excision of non-viable tissue, to help coaptation. However, an important part of nerve repair is to judge the extent of necrotic tissue in specific injuries. In severe cases, caused by for example a gun shot wound, there may be widespread injury to the peripheral nerve components. It can be difficult in the fresh case to evaluate how much of the nerve ends needs to be resected. In

such injuries it is of extreme importance to tidy up the wound and remove all other necrotic tissues to avoid infection. In some cases with severe nerve injuries it may be advisable to delay the nerve reconstruction until all other tissues, such as muscle, have healed properly. However, this is not the case in a sharp transection injury where a primary suture is the best alternative (30).

Another interesting issue is exploration of the radial nerve in patients with radial nerve dysfunction in connection with a humeral shaft fracture. The radial nerve can in such cases be injured or even ruptured (31–34). If the humeral shaft fracture is to be repaired with plates and screws one may consider exploring the dysfunctional radial nerve at the same time. In case one is convinced that the radial nerve is severely lacerated an early repair should be considered based on the neurobiological alterations and impaired axonal outgrowth with time described earlier (3, 6, 13). However, one can not as a general rule recommend a generous exploration of all radial nerves that may have some dysfunction after humeral

shaft fractures (33, 34). It is generally recommended that the radial nerve not be explored within the first three months, although earlier time points can be considered (31), since in the majority of cases a spontaneous recovery can be expected within that time (33, 34). It is wise to regularly and meticulously examine the patients with respect to signs of regeneration, i.e. progressive reinnervation of the radial nerve innervated muscles.

Brachial plexus injuries are worth specific considerations regarding the timing of exploration and reconstruction. Such injuries require extra care since the brachial plexus nerve injury usually is only one of many injuries that such a patient may suffer in connection to, for example, motor cycle accidents. Strict medical priority has to be applied in handling all such injuries. Thus, exploration of the brachial plexus nerve injuries may need to be performed with a delay, although early reconstruction has recently been shown to improve results after the brachial plexus

injury (35); a phenomenon related to for example cell death and efficiency of axonal outgrowth (6, 36).

## TECHNIQUES OF BRIDGING A NERVE DEFECT

In severe injuries of different causes there may be a defect between the severed nerve ends after resection of necrotic tissue of the nerve trunk. As a support for the axons such a defect has to be bridged by a nerve graft (37, 38). A number of different donor nerves, preferably sensory branches, are available. The most common donor nerve is the sural nerve. At harvest it is possible to get a long (from the lateral malleolus up to just below the knee) graft with few branches (37). Other donor nerves are the medial antebrachial cutaneous nerve in the forearm and the terminal branch of the posterior interosseous nerve. The latter two are particularly suitable for digital nerves (37). For digital nerves the use of autologous nerve grafts has been questioned due to potential sequelae after harvesting. Nerve tubes or other alternatives may be selected in such situations.

During the last years different types of alternatives to nerve grafts have become available. However, for most of them only experimental data are accessible. Acellular nerve grafts, used with the purpose of applying a suitable three-dimensional matrix for the outgrowing axons, have been described including acellular nerve allografts which can be prepared by extraction (39, 40). However, no clinical randomized studies have been published describing outcome of such procedures.

For short digital nerve defects longitudinal sutures can be applied (41), where absorbable sutures are used as a guideline for the fibrin matrix formed between the nerve ends. Schwann cells and axons migrate through the fibrin matrix thus bridging the gap. A new perineurium-like structure is also formed around the new nerve trunk.

However, the conventional nerve graft is the autologous nerve graft. Hitherto, autologous sensory nerves have been recommended as donors for nerve grafts since there are few expendable motor nerves, although it has been suggested experimentally that nerve regeneration in motor grafts is more robust than in sensory grafts due to different nerve architecture, like size of Schwann cell basal lamina tubes (42). The nerve graft is usually oriented in a reverse fashion. It should be attached closely between the nerve ends, preferably with any joint the graft should cross in an extended position. Multiple cables of the nerve graft are applied without any tension. One or two sutures is used to maintain coaptation of the nerve grafts and supplementary fibrin glue is often used (e.g. TisseI®). A sufficient number of cables is applied between the severed nerve ends. If possible, individual corresponding fascicles should be bridged by specific cable grafts. Individual cables should not adhere too closely to each other allowing diffusion of oxygen and revascularization. Finally, it is recommendable that the tissue bed on which the graft is applied should have an optimal viability for survival of the Schwann cells (Fig. 3).

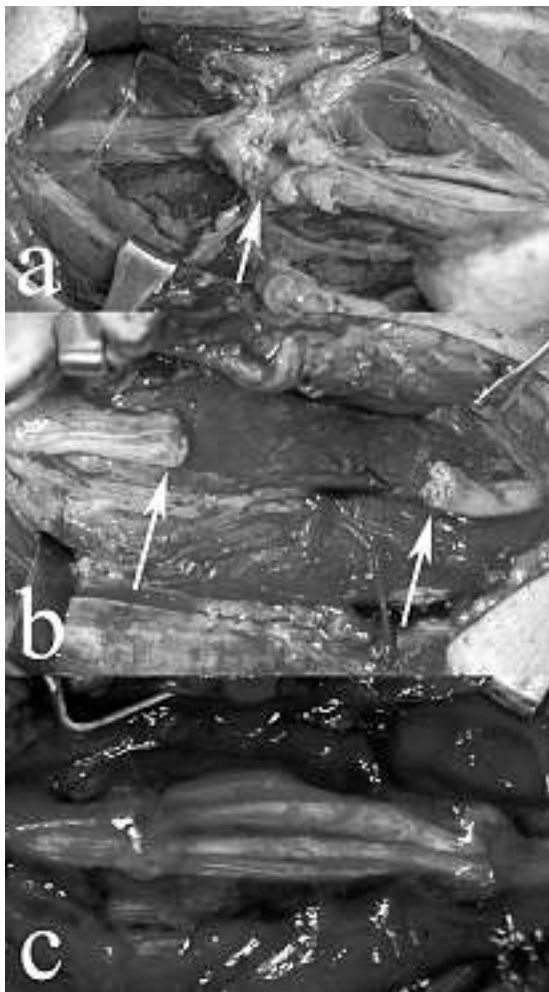


Fig 3. A lacerated ulnar nerve in the forearm after fracture with a scar between the nerve ends (arrow; a). The nerve was explored and scar tissue resected exposing healthy fascicles in the proximal and distal nerve ends (arrows; b). The defect was bridged by several pieces of a sural nerve graft, which was secured by fibrin glue (c). Reproduced by kind permission of Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery.

## NERVE TRANSFERS

During recent years nerve transfers have been more frequently used whereby less important nerve fascicles from a donor nerve are transected, intraneurally dissected and redirected to be attached to a functionally more important injured distal nerve segment (43, 44). Alternatively, a whole distal branch of a nerve (e.g. distal anterior interosseous nerve) can be transected and transferred to an injured distal nerve (e.g. the thenar motor branch) (45). Thus, by the technique of nerve transfer a proximal nerve injury is transformed into the distal one with short regeneration distance to target. The procedure to transfer nerve trunks is frequently used in reconstruction of the brachial plexus, like transfer of intercostal nerves to the musculocutaneous nerve (46), particularly when no proximal nerve roots, as a source of axons, are present.

## END-TO-SIDE NERVE REPAIR

Another technique that has been reintroduced is the end-to-side nerve repair (47). Such a procedure involves attachment of one or two distal nerve ends of an injured nerve end-to-side to an "uninjured" donor nerve. This is done when there are no proximal nerve ends available as sources of axons. Outgrowth of axons from the donor nerve in the end-to-side attached nerve segment probably requires an injury signal to the axons in the donor nerve (48).

## POSTOPERATIVE REGIME AFTER NERVE REPAIR

It is advisable that a nerve repair, a nerve reconstruction by nerve grafts or nerve transfers are protected by immobilisation, which may last from 10–14 days up to six weeks depending on the location of the nerve injury and the risk for tension of the nerve repair. After immobilisation rehabilitation is initiated to achieve full passive and active range of motion. The advancement of the outgrowing axons is followed by the Tinel's sign. In nerve injuries, where motor function is expected after repair or reconstruction, e.g. a radial nerve, reinnervation of the denervated muscle is followed.

Particularly following an injury to a sensory nerve, misdirection of axons is extensive leading to difficulties of the adult brain to interpret the new information from the periphery (49). To remodel and relearn the new language which is spoken by the hand, specific relearning and re-education techniques are initiated (50). Training can be initiated in the early (i.e. before reinnervation of the hand) and in the late (some reinnervation of skin) postoperative phases. An effective relearning process is probably highly influenced by the motivation of the individual patient. In addition, different coping strategies by the patient are important for the patient's ability to handle the effects of the injury.

Rehabilitation of the patients after nerve injury also

includes a meticulous evaluation of the outcome including sensory and motor function as well as other forms of discomfort such as allodynia, cold intolerance and pain (50). These symptoms should carefully be considered and treated. The outcome of nerve repair and nerve reconstruction after nerve injuries is influenced by many factors of which age is probably one of the most prominent ones. Age may explain more than 50% of the variance in functional sensibility after nerve injury (51), but also other factors such as the capacity for verbal learning and visio-spatial logic capacity are crucial. The timing of nerve repair, as pointed out above, is also important since a number of neurobiological factors diminish over time. The type of nerve is significant for the outcome (e.g. poor outcome after repair of a mixed nerve at a proximal location while a pure motor nerve close to target leads to excellent recovery). The type of lesion and level of injury are other components of importance (14). If the motor function is not restored properly tendon transfers may be considered. This is described in another article in this issue.

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## REFERENCES

1. Rosberg HE, Carlsson KS, Hojgard S, Lindgren B, Lundborg G, Dahlin LB: Injury to the human median and ulnar nerves in the forearm—analysis of costs for treatment and rehabilitation of 69 patients in southern Sweden. *J Hand Surg (Br)* 2005;30:35–39
2. Martensson L, Gustavsson P, Dahlin LB, Kanje M: Activation of extracellular-signal-regulated kinase-1/2 precedes and is required for injury-induced Schwann cell proliferation. *Neuroreport* 2007;18:957–961
3. Dahlin LB: The nerve response to injury. In: Upper extremity nerve repair – tips and techniques: A master skills publication. Slutsky D, Ed. ASSH. 2008, pp. 15–28
4. Tsujino H, Kondo E, Fukuoka T, Dai Y, Tokunaga A, Miki K, Yonenobu K, Ochi T, Noguchi K: Activating transcription factor 3 (ATF3) induction by axotomy in sensory and motoneurons: A novel neuronal marker of nerve injury. *Mol Cell Neurosci* 2000;15:170–182
5. Hunt DA, Hossain-Ibrahim K, Mason MR, Coffin RS, Lieberman AR, Winterbottom J, Anderson PN: ATF3 upregulation in glia during Wallerian degeneration: differential expression in peripheral nerves and CNS white matter. *BMC Neurosci* 2004;5:9.
6. Saito H, Dahlin LB: Expression of ATF3 and axonal outgrowth are impaired after delayed nerve repair. *BMC Neurosci* 2008; 9:88
7. Kataoka K, Kanje M, Dahlin LB: Induction of activating transcription factor 3 after different sciatic nerve injuries in adult rats. *Scand J Plast Reconstr Surg Hand Surg* 2007;41:158–166
8. Hall S: The response to injury in the peripheral nervous system. *J Bone Joint Surg (Br)* 2005;87:1309–1319
9. Terenghi G, Calder JS, Birch R, Hall SM: A morphological study of Schwann cells and axonal regeneration in chronically transected human peripheral nerves. *J Hand Surg (Br)* 1998; 23:583–587
10. Sulaiman OA, Gordon T: Effects of short- and long-term Schwann cell denervation on peripheral nerve regeneration, myelination, and size. *Glia* 2000;32:234–246



11. Hoke A, Gordon T, Zochodne DW, Sulaiman OA: A decline in glial cell-line-derived neurotrophic factor expression is associated with impaired regeneration after long-term Schwann cell denervation. *Exp Neurol* 2002;173:77–85
12. Li H, Terenghi G, Hall SM: Effects of delayed re-innervation on the expression of c-erbB receptors by chronically denervated rat Schwann cells in vivo. *Glia* 1997;20:333–347
13. Dahlin LB: Nerve injury and repair: from molecule to man. In: *Peripheral nerve surgery – practical applications in the upper extremity*. Slutsky DJ, Hentz VR, Eds. Churchill Livingstone Elsevier, Philadelphia, 2006, pp. 1–22
14. Dahlin LB: Nerve injuries. *Curr Orthop* 2008;22:9–16
15. Hanz S, Perlson E, Willis D, Zheng JQ, Massarwa R, Huerta JJ, Koltzenburg M, Kohler M, van-Minnen J, Twiss JL, Fainzilber M: Axoplasmic importins enable retrograde injury signaling in lesioned nerve. *Neuron* 2003;40:1095–1104
16. Yudin D, Hanz S, Yoo S, Iavnilovitch E, Willis D, Gradus T, Vuppalandhi D, Segal-Ruder Y, Ben-Yaakov K, Hieda M, Yoneda Y, Twiss JL, Fainzilber M: Localized regulation of axonal RanGTPase controls retrograde injury signaling in peripheral nerve. *Neuron* 2008;59:241–252
17. Bontioti EN, Kanje M, Dahlin LB: Regeneration and functional recovery in the upper extremity of rats after various types of nerve injuries. *J Peripher Nerv Syst* 2003;8:159–168
18. Lund LM, Machado VM, McQuarrie IG: Increased beta-actin and tubulin polymerization in regrowing axons: relationship to the conditioning lesion effect. *Exp Neurol* 2002;178:306–312
19. Ma J, Novikov LN, Kellerth JO, Wiberg M: Early nerve repair after injury to the postganglionic plexus: an experimental study of sensory and motor neuronal survival in adult rats. *Scand J Plast Reconstr Surg Hand Surg* 2003;37:1–9
20. McKay Hart A, Wiberg M, Terenghi G: Pharmacological enhancement of peripheral nerve regeneration in the rat by systemic acetyl-L-carnitine treatment. *Neurosci Lett* 2002;334:181–185
21. Wilson AD, Hart A, Brannstrom T, Wiberg M, Terenghi G: Delayed acetyl-L-carnitine administration and its effect on sensory neuronal rescue after peripheral nerve injury. *J Plast Reconstr Aesthet Surg* 2007;60:114–118
22. West CA, Hart AM, Terenghi G, Wiberg M: Analysis of the dose-response of N-acetylcysteine in the prevention of sensory neuronal loss after peripheral nerve injury. *Acta Neurochir Suppl* 2007;100:29–31
23. Brandt J, Dahlin LB, Kanje M, Lundborg G: Spatiotemporal progress of nerve regeneration in a tendon autograft used for bridging a peripheral nerve defect. *Exp Neurol* 1999;160:386–393
24. Scherman P, Lundborg G, Kanje M, Dahlin LB: Neural regeneration along longitudinal polyglactin sutures across short and extended defects in the rat sciatic nerve. *J Neurosurg* 2001;95:316–323
25. Jabaley M: Primary nerve repair. In: *Peripheral nerve surgery: Practical applications in the upper extremity*. Slutsky DJ, Hentz VR, Eds. Churchill Livingstone Elsevier, Philadelphia, 2006, pp. 23–38
26. Lundborg G, Rosen B, Dahlin L, Holmberg J, Rosen I: Tubular repair of the median or ulnar nerve in the human forearm: a 5-year follow-up. *J Hand Surg (Br)* 2004;29:100–1007
27. Dahlin LB, Anagnostaki L, Lundborg G: Tissue response to silicone tubes used to repair human median and ulnar nerves. *Scand J Plast Reconstr Surg Hand Surg* 2001;35:29–34
28. Weber A, Breidenback WC, Brown RE, Jabaley ME, Mass DP: A randomized prospective study of polyglycolic acid conduits for digital nerve reconstruction in humans. *Plast Reconstr Surg* 2000;106:1036–1045
29. Brandt J, Nilsson A, Kanje M, Lundborg G, Dahlin LB: Acutely-dissociated Schwann cells used in tendon autografts for bridging nerve defects in rats: a new principle for tissue engineering in nerve reconstruction. *Scand J Plast Reconstr Surg Hand Surg* 2005;39:321–325
30. Birch R, Raji A: Repair of median and ulnar nerves – primary suture is best. *J Bone Joint Surg* 1991;73B:154–157
31. Thomsen NO, Dahlin LB: Injury to the radial nerve caused by fracture of the humeral shaft: Timing and neurobiological aspects related to treatment and diagnosis. *Scand J Plast Reconstr Surg Hand Surg* 2007;41:153–157
32. Ekholm R, Ponzer S, Tornkvist H, Adami J, Tidermark J: Primary radial nerve palsy in patients with acute humeral shaft fractures. *J Orthop Trauma* 2008;22:408–414
33. DeFranco MJ, Lawton JN: Radial nerve injuries associated with humeral fractures. *J Hand Surg (Am)* 2006;31:655–663
34. Shao YC, Harwood P, Grotz MR, Limb D, Giannoudis PV: Radial nerve palsy associated with fractures of the shaft of the humerus: a systematic review. *J Bone Joint Surg Br* 2005;87:1647–1652
35. Jivan S, Kumar N, Wiberg M, Kay S: The influence of pre-surgical delay on functional outcome after reconstruction of brachial plexus injuries. *J Plast Reconstr Aesthet Surg* 2008;May 15 (Epub ahead of print)
36. Jivan S, Novikova LN, Wiberg M, Novikov LN: The effects of delayed nerve repair on neuronal survival and axonal regeneration after seventh cervical spinal nerve axotomy in adult rats. *Exp Brain Res* 2006;170:245–254
37. Slutsky D: A practical approach to nerve grafting in the upper extremity. In: *Peripheral nerve surgery – practical applications in the upper extremity*. Slutsky DJ, Hentz VR, Eds. Churchill Livingstone Elsevier, Philadelphia, 2006, pp. 61–80
38. Millesi H: Nerve grafting. In: *Peripheral nerve surgery – practical applications in the upper extremity*. Slutsky D, Hentz VR, Eds. Churchill Livingstone Elsevier, Philadelphia, 2006, pp. 39–59
39. Neubauer D, Graham JB, Muir D: Chondroitinase treatment increases the effective length of acellular nerve grafts. *Exp Neurol* 2007;207:163–170
40. Krekoski CA, Neubauer D, Zuo J, Muir D: Axonal regeneration into acellular nerve grafts is enhanced by degradation of chondroitin sulfate proteoglycan. *J Neurosci* 2001;21:6206–6213
41. Scherman P, Kanje M, Dahlin LB: Sutures as longitudinal guides for the repair of nerve defects--influence of suture numbers and reconstruction of nerve bifurcations. *Restor Neurol Neurosci* 2005;23:79–85
42. Moradzadeh A, Borschel GH, Luciano JP, Whitlock EL, Hayashi A, Hunter DA, Mackinnon SE: The impact of motor and sensory nerve architecture on nerve regeneration. *Exp Neurol* 2008;212:370–376
43. Mackinnon SE, Colbert SH: Nerve transfers in the hand and upper extremity surgery. *Tech Hand Up Extrem Surg* 2008;12:20–33
44. Oberlin C, Ameur NE, Teboul F, Beaulieu JY, Vacher C: Restoration of elbow flexion in brachial plexus injury by transfer of ulnar nerve fascicles to the nerve to the biceps muscle. *Tech Hand Up Extrem Surg* 2002;6:86–90
45. Vernadakis AJ, Humphreys DB, Mackinnon SE: Distal anterior interosseous nerve in the recurrent motor branch graft for reconstruction of a median nerve neuroma-in-continuity. *J Reconstr Microsurg* 2004;20:7–11
46. Malessy MJ, Bakker D, Dekker AJ, Van Duk JG, Thomeer RT: Functional magnetic resonance imaging and control over the biceps muscle after intercostal-musculocutaneous nerve transfer. *J Neurosurg* 2003;98:261–268
47. Bontioti E, Kanje M, Lundborg G, Dahlin LB: End-to-side nerve repair in the upper extremity of rat. *J Peripher Nerv Syst* 2005;10:58–68
48. Bontioti E, Dahlin LB, Kataoka K, Kanje M: End-to-side nerve repair induces nuclear translocation of activating transcription factor 3. *Scand J Plast Reconstr Surg Hand Surg* 2006;40:321–328
49. Lundborg G, Bjorkman A: Cortical effects of nerve injury. In: *Upper extremity nerve repair – tips and techniques: A master skills publication*. Slutsky D, Ed. ASSH.2008, pp. 29–37
50. Rosen B, Lundborg G: Sensory re-education following nerve repair. In: *Upper extremity nerve repair – tips and techniques: A master skills publication*. Slutsky D, Ed. ASSH.2008, pp. 159–178
51. Rosén B, Lundborg G, Dahlin LB, Holmberg J, Karlsson B: Nerve repair: Correlation of restitution of functional sensibility with specific cognitive capacities. *J Hand Surg* 1994;19B:452–458

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