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Pathophysiology of Peripheral Nerve Injury

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1. Introduction

Peripheral nervous system (PNS) is a complex construction, which serves dual purpose. Firstly, it disseminates information from the central nervous systems and ensures that this information is interpreted to the target end - organs. Secondly, it collects information from the periphery, translates it to nerve signals, processes it and feeds it back to the central nervous system. The PNS consists of a complex arborisation of peripheral nerves. In order to set a stage for the information that will be presented further on, I will shortly review the relevant anatomy first. The peripheral nerves are long extension of neuronal cells, which cells bodies are located in the spinal chord and dorsal root ganglia (spinal nerves) or in the brain (cranial nerves). The peripheral nerve consists of nerve fibres and supportive connective tissue. The connective tissue is organised longitudinally surrounding the nerve fibres and serves a double function. Firstly, it provides mechanical support for the nerve fibres to withstand stretching and compression during the body movements. Secondly, it contains blood vessels – vasa nervorum, which ensure trophic support for the fibres (Gray 1995). The connective tissue is organised in three "layers". The outermost layer – epineurium – is a thick layer of connective tissue which ensheaths the nerve and isolates it from the external environment (Fig.1). The vasa nervorum are continued within this layer and these vessels communicate abundantly with the network of arterioles and venules found in the connective tissues in the depth of the nerve. The amount of epineurium differs depending on the individual, thickness of the nerve and location. There is an evidence that epineurium is thicker around joints (Sunderland 1978). Deep to epineurium, the axonal fibres are organised in one (unifascicular) or more (multifascicular) fascicles. The fascicles are enclosed within the second layer of connective tissue – perineurium (Fig.1). The perineurium is a thick and mechanically strong layer, which is composed of epithelium-like cells and collagen fibres. The cells are typically organised in several layers separated by collagen with ample vascular structures running longitudinally (Thomas and Jones 1967). This stratification gives perineurium a great endurance and ability to withstand a pressure in excess of 200 mmHg (Selander and Sjöstrand 1978). Deep to perineurium the endoneurium is found (Fig. 1). It consists of loose collagenous matrix enveloping the nerve fibres and providing further protection from mechanical forces. The endoneurium also contains several important cell types. The most abundant one are Schwann cells, followed by fibroblasts, endothelial-like cells, macrophages and mastocytes (Causey and Barton 1959). It is important to note that endoneurium contains ample extracellular matrix and fluid, which is contained at a slightly higher pressure that that surrounding perineurium (Myers et al. 1978). The reason for that is unknown, although we can speculate that it protects

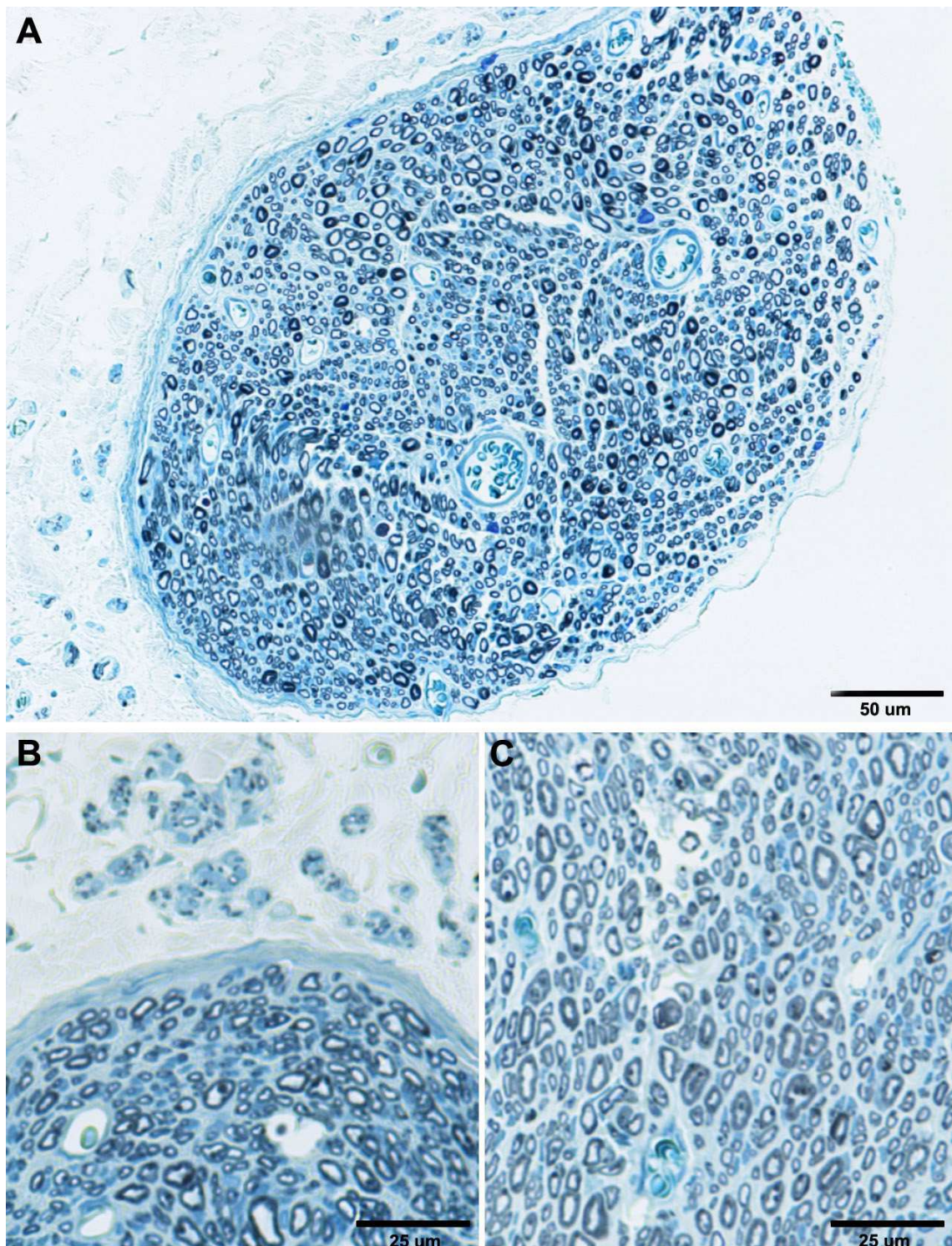endoneurial space from possible contamination by toxic substances external to the epineural space.

Fig. 1. Ultrastructure of the peripheral nerve.

(a) Toluidine blue stained transverse section through peripheral nerve of rat.
(b) Detail on thick epineurium enveloping the nerve
(c) Detail on area with peri- and endoneurium.

When talking about the injury to the nervous system, it is essential to consider all parts of this system and also end organs, which are dependent on it. Thus, this review will focus separately on neural cells, sensory organs and muscle.

1.1 Response of the neural cells

The damage to the neural cells is the most obvious consequence of the injury to the peripheral nerve. As mentioned above, the nerve is essentially a multi-strand cord-like structure, which keeps the nerve fibres organised and protected from the external forces. With the cell bodies being located in the spinal cord and dorsal root ganglia, all the injuries to the nerves are happening at the level of cellular processes – axons. Perhaps the only exception to this statement is roots avulsion from spinal cord, for example during brachial plexus injury. The nerve injury divides neurons into a part, which is proximal and a part, which is distal to the injury site. These two parts differ significantly from each other, as far as the reaction to the injury is concerned.

1.1.1 Distal to the injury site (Wallerian degeneration)

More than 160 years have passed since the first report describing the reaction of distal nerve stump to axotomy. The original work was performed by Augustus Waller and was presented to the Royal Society of London in 1850. Waller was studying injuries to glossopharyngeal and hypoglossal nerves in frogs. It is obligatory to quote an excerpt from his original report here (Waller 1850):

"During the four first days, after section of the hypoglossal nerve, no change is observed in its structure. On the fifth day the tubes appear more varicose than usual, and the medulla (term used to describe axons) more irregular. About the tenth day medulla forms disorganized, fusiform masses at intervals, and where the white substance of SCHWANN cannot be detected. These alterations, which are most evident in the single tubules, may be found also in the branches. After twelve or fifteen days many of the single tubules have ceased to be visible, their granular medulla having been removed by absorption. The branches contain masses of amorphous medulla."

This process of disintegration of distal axonal stump after injury is termed Wallerian degeneration. It is a recognized consequence of a mechanical (but not only) insult to the nerve. Wallerian degeneration starts almost immediately after axotomy and lasts 3 – 6 weeks (Geuna et al. 2009). The first sign is disintegration of axons, which starts during first 24 to 48 hours (Stoll et al. 1989). The beginning of this process is characterised by granulation within axoplasma caused by proteolysis of microtubules and neurofilaments (Lubińska 1982, Schlaepfer 1977). This is caused by a rapid activation of axoplasmatic proteolyses, which occurs as a response to intracellular calcium influx (George, Glass, and Griffin 1995, Schlaepfer and Bunge 1973). An early activation of ubiquitin-proteasome system has been also shown to play an important role here (Ehlers 2004). Among all the cytoskeletal structures, the microtubules are thought to disintegrate first (Watts, Hoopfer, and Luo 2003, Zhai et al. 2003). The loss of microtubular structures then leads to impediment of axonal transport and further accelerates the degeneration process. The disintegration of neurofilaments follows shortly and is usually completed within 7 – 10 days. During this time, the partially disrupted neurofilaments can be detected in the axoplasma only to

completely disappear shortly afterwards. One more important point, which needs to be made, is the direction of the Wallerian degeneration. It seems that the process is bidirectional. It starts in the zone just below the injury and progresses distally while at the same time starts at the distal axonal termini (Waxman 1995). Despite the very brisk initiation of degenerative changes, the distal nerve stump preserves its excitability for a considerable period of time. When the transacted axons are stimulated distal to the injury zone, it is often possible to record nerve potentials for up to 10 days. Therefore, it is very important for this period of refractory excitability to finish, before accurate estimate of the nerve injury extent can be made by electrophysiological methods.

The processes, which we have discussed so far, were limited to the axon and its inherent ability to degenerate after injury. To have the full picture of the Wallerian degeneration, we also need to talk about other cells, which participate and play an integral role in it. In particular, the role of Schwann cells and macrophages is critical for the Wallerian degeneration to take place. The Schwann cells are very sensitive to the loss of contact with axon. In case of dennervation, the Schwann cells change from "supportive" to "reactive" phenotype. They stop producing myelin (LeBlanc and Poduslo 1990). The continuing proliferation of Schwann cells leads to formation of Bands of Bungers, which purpose is thought to be guidance of the regrowing axons (further discussed in the regeneration subchapter) (Liu, Yang, and Yang 1995). It seems that this phenotypic switch is, at least partly, a response to neuregulin secretion from the transacted axons (Esper and Loeb 2004). Activated Schwann cells were found to secret a wide range of immunologically active substances. In particular, Interleukin (IL) -1B, IL – 6, IL – 10 and Leukaemia Inhibitory Factor (LIF) were detected abundantly at the injury site in the first few days after injury (Bolin et al. 1995, Jander et al. 1996, Jander and Stoll 1998, Kurek et al. 1996). These substances are responsible for attracting immune cells into the distal nerve stump and orchestrating their function. It was shown, that in the first two days after nerve injury macrophages and T cells start to infiltrate injury zone, which culminates in infiltration of the entire distal stump by day 4 (Brück 1997, Perry, Brown, and Gordon 1987). They are responsible for phagocytosis of the axonal debris and myelin sheaths residua released from the disintegrating axons and thus finishing the breakdown and elimination of axons.

1.1.2 Proximal to the injury site (proximal end degeneration)

The immediate consequence of axotomy is partial retraction of the proximal stump (Cajal 1928) leaving empty endoneurial tubes lined by Schwann cells. The distance to which the proximal stump retracts is usually one or two nodes of Ranvier, but that depends on severity and character of injury. Within the same timeframe the injured axons also seal their injured axolemma to prevent axoplasma leakage. Shortly after retraction and as early as hours after axotomy, the proximal stump starts to produce regenerative sprouts (McQuarrie 1985, Meller 1987, Friede and Bischhausen 1980). While these sprouts are forming the cut tip of the axon swells up, containing endoplasmatic reticulum, mitochondria and microtubules. This swelling contains products accumulating in the tip of the stump because of disrupted anterograde axonal transport. One important event happening in the area of the swelling is reorganisation of microtubular cytoskeleton. In the normal axon the microtubules are organised longitudinally and all point distally along the axon. After axotomy the arrangement of microtubules changes and they point against each other (Erez et al. 2007).

This swelling is very probably giving the basis for development of axonal end-bulbs, which occurs within 24 – 48 hours after the injury. The relation between axonal endbulb and axonal growth cone remains not fully understood (Goldberg, Frank, and Krayanek 1983). A recent report suggests that depending on the local environment, the injured axons either form regenerative growth cones or incompetent endbulbs (Kamber, Erez, and Spira 2009). The successful formation of the growth cone is the ultimate goal of the proximal nerve stump, as this will be the starting point of the nerve regeneration (see below).

1.1.3 Cell body response

The neurons, which axons were injured and ended up in Wallerian degeneration have lost a substantial part of their cellular mass. Although we expect them to re-grow their lost parts and re-establish the functional connection with their end organ, the situation is not always so favourable. It seems, that the outcome is influenced by location of the lesion in relation to cell body, type of neuron, physical age and local availability of trophic factors. The most extreme outcome of nerve axotomy is cellular death of the injured neuron. The proportion of neuronal cell death in dorsal root ganglia after sciatic nerve lesion in rodents has been reported to be 10 – 30 % (Ygge 1989, Groves et al. 1997). The number is much lower in motoneurons, where no significant neuronal death has been observed (Vanden Noven et al. 1993). However, the situation is dramatically different if the nerve (or ventral root) has been avulsed from the spinal chord. In this case the motoneuronal death can be as high as 80% (Martin, Kaiser, and A C Price 1999, Koliatsos et al. 1994).

There are several morphological changes in the surviving neurons after axotomy. The most obvious one is chromatolysis, which is dissolution of the Nissle substance (Cotman 1978, Kreutzberg 1995). The Nissle substance is a synonym for rough endoplasmatic reticulum containing mRNA, which has blue and dotty appearance on haematoxylin eosin stain. It is normally located in the centre of the neuron. The chromatolysis starts within hours of injury and peaks from 1 – 3 weeks. It usually resolves with reinnervation and the process is more prolonged and intensified if the distal reinnervation does not occur. The chromatolysis seamlessly continues either to regeneration or to neuronal death (Martin, Kaiser, and Price 1999). It is not entirely understood what makes the neuron to initiate chromatolysis. It seems that local synthesis of regulatory proteins on the axonal level and their linking to the dynein retrograde motor are at the start of the process (Hanz and Fainzilber 2006). Another early event after axotomy is swelling of the neuronal body and increase of nucleolar size. Later, the nucleus is displaced under the cell membrane and if the reinnervation does not occur, the neuron undergoes atrophy. One more important morphological change after neuronal injury is a reduction of dendritic arborisation. This dendritic retraction leads to a decrease of the number of synaptic connections of the injured neuron and to a functional isolation of it (Purves 1975, Brännström, Havton, and Kellerth 1992a). There is an evidence the motoneurones rebuild their dendritic complex following the reinnervation of target muscle (Brännström, Havton, and Kellerth 1992b). In contrast, in permanent axotomy this does not happen (Brännström, Havton, and Kellerth 1992a).

Apart from the morphological changes discussed so far, there is also a great shift on the functional cellular level. After axotomy, the surviving neurons switch from signal transmitter "program" to regenerative "program", or as Fu and Gordon put it from "signalling mode" to "growing mode" (Fu and T Gordon 1997). The survival of the cell and

the mode switch are the first critical steps taken by the neuron towards regeneration. The switch brings changes to protein expression levels in the way that signalling-associated proteins become downregulated and growth-associated proteins and structural components of the cell become upregulated. Gene expression studies have demonstrated changes in expression patterns of hundreds of genes - the function of many is still yet to be explored (Kubo et al. 2002, Bosse et al. 2006). There seems to be a similarity between these newly found expression patterns and protein expression in developing neurons during embryological development. A group of growth-associated proteins, such as GAP-43 (Skene et al. 1986), are upregulated during the axonal growth phase up to 100 times and then their expression drops down upon reinnervation (Karns et al. 1987, Skene et al. 1986). Also, the expression of cytoskeletal component genes follows the developmental pattern. The production of neurofilaments gets tuned down (Oblinger and Lasek 1988, Hoffman et al. 1987) whereas the production of tubulins steeply increases (Miller et al. 1989, Hoffman and Cleveland 1988). Following is the recapitulation of changes in gene expression in the most important gene categories (Navarro 2009). Upregulated genes include:

- Transription factors (c-fos, c-jun, ATF3, NFkB, CREB, STAT)
- Neurotrophic factors (NGF, BDNF, GDNF, FGF)
- Neurotrophic receptors (Trk, Ret, P75)
- Cytokines (TNFa, MCP1)
- Growth associated proteins (GAP43)

And the downregulated genes are:

- Neurofilaments
- Neurotransmitters
- Postsynaptic receptors

This is by no means an exhaustive list, but should serve only as a demonstration of the philosophy behind gene expression alteration following nerve injury.

1.2 Response of the end organs and connective tissues

The multitude of functions that nerves fulfil is only possible because of a fine-tuned crosstalk between the nerve and its end organs. It is important to note here, that the nerve acts merely as an interface between the central nervous system and peripheral organs. Thus, for the nerve to function as intended it must be connected to the end organs. The end organs must not only function properly, but also have to effectively communicate with the nerve. After the nerve injury this co-dependent communication circuit gets disrupted. If we look at the nerve regeneration as a process of re-establishing this communication, we also need to consider the end organs and their reaction to the nerve injury. This will be in discussed in this subchapter.

1.2.1 Response of muscle

Reaction of the muscle to the dennervation takes place on several levels. The dennervated muscle changes its structure and its electrophysiological and biochemical properties. It has not been fully explained why these changes occur. It is probably a mixture of inactivity and loss of trophic stimuli from the neurons (Midrio 2006). The principal structural change is atrophy of individual muscle fibres with loss of muscle weight. The weight may decrease to

as low as 30% of the muscle original weight (Fu and T Gordon 1995). Under light microscope the muscle fibres form nuclear knots, which are chains of nuclei with very little surrounding sarcoplasm. On ultrastructural level we can detect disruption of myofibrils and disorganisation of sarcomeres. Electrophysiological tests will show decline in Compound Muscle Action Potential (CMAP), which normally recovers with reinnervation. During regeneration the muscle motor units can significantly enlarge. This happens due to collateral sprouting, where one neuron will eventually innervate a higher number of motor plates then it did originally (Fu and T Gordon 1995). On biochemical level, the dennervated muscles show decreased uptake of glucose, impaired binding of insulin, decrease of intramuscular glycogen and also alteration of glycolytic enzymes (Burant et al. 1984, Donaldson, Evans, and Harrison 1986, DuBois and Max 1983).

1.2.2 Response of sensory organs

The response of the sensory organs is much less studied and understood than that of the muscle. A successful reinnervation of cutaneous sensory organs depends of a small subset of Schwann cells found at the terminal ending of neural fibres. The dennervation of the sensory organs results in the survival of these Schwann cells along with the capsular structures of sensory organs (Dubový and Aldskogius 1996), which are thought to guide the axonal regrowth towards their appropriate targets.

2. Axonal regeneration after peripheral nerve injury

As discussed above, the first wave of axonal sprouting occurs as soon as hours after axotomy (Fawcett and Keynes 1990, Mira 1984). The transected axons produce a great amount of terminal and collateral sprouts, which are progressing down the endoneurial tube while being in close contact with the Schwann cells (Nathaniel and Pease 1963, Haftek and Thomas 1968). This first wave of axonal sprouting is followed by a second wave about two days later (Cajal 1928, Mira 1984, Cotman 1978). It has been observed that axons may branch once they reach the distal stump, where one axon may give rise to several branches (Jenq, Jenq, and Coggeshall 1987, Bray and Aguayo 1974). The early regenerating axons are growing in the environment, which contains Schwann cells with their basal lamina, fibroblasts, collagen, immunocompetent cells and axonal debris from degenerating axons. The Schwann cells and their basal lamina play a crucial and indispensable role in the nerve regeneration. It was shown that if the Schwann cells are not present in the distal stump, the regeneration occurs very slowly. This is only thanks to a support of the Schwann cells migrating from the proximal stump and accompanying the regenerating axons (Gulati 1988, Hall 1986a). If the migration of the Schwann cells into the distal nerve stump is prohibited (such as by a cytotoxic agent), the axons fail to regenerate completely (Hall 1986b). As mentioned above, the Schwann cells react swiftly to the loss of axonal contact by proliferation and assisting in breaking down the myelin sheaths. While multiplying, they also migrate and align themselves into longitudinal columns called bands of Bungner (Waxman 1995, Duce and Keen 1980, Lundborg et al. 1982). The bands of Bungner are physical guides for regenerating axons. The axons first grow through the injury zone and then into the bands of Bungner. In order for the regeneration outcome to achieve the pre-injury state, the axons should ideally grow back into their corresponding columns. However, the studies on early behaviour of regenerating axons showed that this is not

happening. Axons send several regenerative sprouts, which can grow in multitude of directions and encounter of up to 100 bands of Bungner (Witzel, Rohde, and Brushart 2005). Some of the axons then grow into them, whereas others may grow freely into the connective tissue of the nerve, or take an extraneural course. In this setting, the choice of final regeneration pathway becomes only a matter of chance. This process is termed axonal misdirection and can significantly hamper the regeneration process. If we consider a situation where a motor fiber grows into the pathway belonging originally to a sensory neuron, this will lead into the failure of functional restoration (Molander and Aldskogius 1992, Bodine-Fowler et al. 1997). It seemed, that there was a preferential affinity of motoneurons to reinnervate motor pathways (Brushart 1993), although a more recent report did not detect any differences in motor against sensory regrowth (Robinson and Madison 2004). One way to reduce the misdirection, which is fully in our hands, is a meticulous surgical technique. It is imperative to use an operating microscope to minimise the impact of a gross misalignment of nerve stumps.

Apart from providing a mechanical guidance for the regenerating axons, the Schwann cells are also responsible for humoral stimulation of the neuronal outgrowth. The expression of NGF is stimulated in Schwann cells shortly after nerve injury (Heumann 1987). This happens very probably as a response to Interleukin-1 secretion by macrophages (Lindholm et al. 1987). Also, the expression of Neurotrophin 3, 4, 5, 6 as well as Brain – Derived Neurotrophic factor sharply increase (Funakoshi et al. 1993). The advancement of axons is further facilitated by growth – promoting molecules, such as laminin and fibronectin (Baron-Van Evercooren et al. 1982, Rauvala et al. 1989). Several studies also demonstrated positive involvement of adhesion molecules, such as neural cell adhesion molecule (NCAM), neural – glia cell adhesion molecule (NgCAM), integrins and cadherins (Walsh and Doherty 1996, Seilheimer and Schachner 1988, Bixby, Lilien, and Reichardt 1988, Hoffman et al. 1986).

In case of myelinated axons, myelination starts as early as eight days after the injury. The remyelination is thought to recapitulate events from the embryonic development. The trigger for the start of myelination is axonal radial growth and reaching a certain diameter. In development it is around 2 μm (Armati 2007). The Schwann cells then rotate around the axon in their endoneurial tube and form a myelin layer around a length of axon, which will correspond to an intermodal segment. It is important to note, that there is a constant relation of 1:1 between a number of cells and internodal segments – i.e. one internodal segment is always myelinated by only one Schwann cell. The internodal segments tend to be shorter in regenerated nerves, in comparison to the developing nerves (Vizoso and Young 1948, Ghabriel and Allt 1977, Minwegen and Friede 1985). This is probably an explanation for decreased conduction velocity in regenerated nerves (Cragg and Thomas 1964). The information whether the myelination will occur or not is stored in the axons. The Schwann cells have an ability to detect that and selectively myelinate appropriate axons (Aguayo et al. 1976, Weinberg and Spencer 1975).

3. Classification of nerve injuries

3.1 Seddon's classification

Under normal circumstances, the nerves remain connected with their innervation targets during the whole life of an individual. The most common disturbance to this status quo is a

nerve damage by mechanical forces, which results in a loss of ability of the nerve to transfer stimuli. These forces can act through compression, traction, laceration and direct injection into the nerve. Moreover, the nerve can get damaged by thermal noxae, electric current, radiation and metabolic disorders. As a result of the injury the CNS completely, or partially, looses the ability to communicate with the neural end organs. The extent to which this happens is greatly variable and depends on the degree of damage to the nerve. The first classification of the severity of nerve injury was published by Seddon (Seddon 1943) and was based on his extensive experience with war victims. He classified the nerve injuries to three degrees, neuropraxia, axonotmesis and neurotmesis and defined the terms as follows:

1. *Neurotmesis* describes the state of a nerve in which all essential structures have been sundered. There is not necessarily an obvious anatomical gap in the nerve; indeed, the epineural sheath may appear to be in continuity, although the rest of the nerve at the site of damage has been completely replaced by fibrous tissue. But the effect is the same as if anatomical continuity had been lost. Neurotmesis is therefore of wider applicability than division.
2. *Axonotmesis*—here the essential lesion is damage to the nerve fibers of such severity that complete peripheral degeneration follows; and yet the epineurium and more intimate supporting structures of the nerve have been so little disturbed that the internal architecture is fairly well preserved. Recovery is spontaneous, and of good quality, because the regenerating fibers are guided into their proper paths by their intact sheaths.
3. *Neuropraxia* is used to describe those cases in which paralysis occurs in the absence of peripheral degeneration. It is more accurate than *transient block* in that the paralysis is often of considerable duration, though recovery always occurs in a shorter time than would be required after complete Wallerian degeneration; it is invariably complete.

3.1.1 Neuropraxia

Neuropraxia is a situation where the nerve (or more commonly a segment of it) looses its ability to propagate action potential while the structural continuity of the axons is fully preserved. The condition is associated with segmental demyelination of the nerve fibers. Because the degree of myelination differs depending on the type of nerve fibers, so does the extent of functional loss and return. The motor fibers are the most susceptible and their function is lost first and regained last, whereas pain and sympathetic fibers are the opposite (Sunderland 1978). Typical example of this type of nerve injury is sleeping with the pressure on the nerve, also called the "Saturday night palsy". This type of injury usually recovers within 12 weeks without any intervention.

3.1.2 Axonotmesis

Axonotmesis is an injury resulting in the loss of axonal continuity without any damage to the connective tissue structures within the nerve. Full Wallerian degeneration and axonal regrowth occur here and a Tinnel's sign accompanies the regeneration. The recovery of function is usually very good, although not as good as in neuropraxia. Surgical intervention is normally not necessary.

3.1.3 Neurotmesis

Damage to the neural connective tissue structures, including endoneurium, perineurium and / or epineurium is termed neurotmesis. Again, Wallerian degeneration and axonal regrowth occur and Tinnel's sign is possible to elicit over the injured nerve. The regeneration process here is hampered by axonal misdirection, loss of nerve/blood barrier and intraneural scarring. Injuries interrupting peri- and epineurium require surgical intervention. The outcome is generally worse than in axonotmesis. This, however, also depends on the relative location from the innervation target and in general it is difficult to predict.

3.2 Sunderland's classification

Early work of Sunderland brought about a much deeper understanding of the nerve ultrastructure (Sunderland, 1947, Sunderland and Bradley 1949). This offered an explanation for a wide variety of clinical findings and outcomes in the neurotmesis category. Natural following of this line of thought was extension of the Seddon's classification, which was formalised by Sutherland (Sunderland 1978). In the new classification the types I and II correspond to neuropraxia and axonotmesis respectively. Type III is an injury involving axons and endoneurium while perineurial and epineurial structures are intact. Sunderland's type IV injury is associated with division of axon, endoneurial and perineurial structures. This is a more significant injury, which often leads to intraneural scarring and requires surgical intervention to ensure the best possible outcome. Finally, type V of Sunderland's classification is a total division of the nerve trunk where all the neuronal and connective tissue structures are interrupted. It is important to note that in real clinical situation nerve injury is often a combination of more than one type of injury. This mixed pattern injury has been classed as a type VI, which was added to the original classification at a later date (Mackinnon 1988).

3.3 Correlations among the grade of injury, clinical and electrophysiological findings and potential for functional recovery

The correlations are found in the following Table 1:

Seddon	Neuropraxia	Axonotmesis	Neurotmesis	Neurotmesis	Neurotmesis
Sunderland	Type I	Type II	Type III	Type IV	Type V
Pathological findings	Anatomical continuity preserved Selective demyelination of the injury zone	Axonal continuity disrupted (together with myelin sheath)	Axonal and endoneurium continuity disrupted	Axonal, endoneurium and perineurium continuity disrupted	Complete division of the nerve
Wallerian degeneration	No	Yes	Yes	Yes	Yes
Motor paralysis	Complete	Complete	Complete	Complete	Complete
Sensory paralysis	Often partially spared	Complete	Complete	Complete	Complete
Autonomic paralysis	Much of the function spared	Complete	Complete	Complete	Complete
Muscle atrophy	Very little	Progressive with time	Progressive with time	Progressive with time	Progressive with time

Seddon	Neuropraxia	Axonotmesis	Neurotmesis	Neurotmesis	Neurotmesis
Sunderland	Type I	Type II	Type III	Type IV	Type V
Tinnel's sign	Absent	Present	Present	Present	Present
Electrophysiol ogical findings	Normal conduction proximal and distal to injury site No conduction through injury site No fibrilation waves	No conduction distal to injury site Fibrilation waves present	No conduction distal to injury site Fibrilation waves present	No conduction distal to injury site Fibrilation waves present	No conduction distal to injury site Fibrilation waves present
Spontaneous recovery	Complete	Complete	Variable	None	None
Surgery needed?	No	No	Varies	Yes	Yes
Rate of recovery	Days (up to 3 months)	Slow – 1 mm per day	Slow – 1 mm per day	Only after surgical repair - 1 mm per day	Only after surgical repair - 1 mm per day

Table 1. Classifications of nerve injuries and their correlation with clinical, pathological and electrophysiological findings.

4. References

Aguayo, A J, J Epps, L Charron, and G M Bray. 1976. "Multipotentiality of Schwann cells in cross-anastomosed and grafted myelinated and unmyelinated nerves: quantitative microscopy and radioautography." *Brain Research* 104 (1) (March 5): 1-20.

Armati, Patricia. 2007. The biology of Schwann cells : development, differentiation and immunomodulation. Cambridge, UK: Cambridge University Press.

Baron-Van Evercooren, A, H K Kleinman, S Ohno, P Marangos, J P Schwartz, and M E Dubois-Dalcq. 1982. "Nerve growth factor, laminin, and fibronectin promote neurite growth in human fetal sensory ganglia cultures." *Journal of Neuroscience Research* 8 (2-3): 179-193.

Bixby, J L, J Lilien, and L F Reichardt. 1988. "Identification of the major proteins that promote neuronal process outgrowth on Schwann cells in vitro." *The Journal of Cell Biology* 107 (1) (July): 353-361.

Bodine-Fowler, S C, R S Meyer, A Moskovitz, R Abrams, and M J Botte. 1997. "Inaccurate projection of rat soleus motoneurons: a comparison of nerve repair techniques." *Muscle & Nerve* 20 (1) (January): 29-37.

Bolin, L M, A N Verity, J E Silver, E M Shooter, and J S Abrams. 1995. "Interleukin-6 production by Schwann cells and induction in sciatic nerve injury." *Journal of Neurochemistry* 64 (2) (February): 850-858.

Bosse, Frank, Kerstin Hasenpusch-Theil, Patrick Küry, and Hans Werner Müller. 2006. "Gene expression profiling reveals that peripheral nerve regeneration is a consequence of both novel injury-dependent and reactivated developmental processes." *Journal of Neurochemistry* 96 (5) (March): 1441-1457.

Brännström, T, L Havton, and J O Kellerth. 1992a. "Changes in size and dendritic arborization patterns of adult cat spinal alpha-motoneurons following permanent

axotomy." *The Journal of Comparative Neurology* 318 (4) (April 22): 439-451. 1992b. "Restorative effects of reinnervation on the size and dendritic arborization patterns of axotomized cat spinal alpha-motoneurons." *The Journal of Comparative Neurology* 318 (4) (April 22): 452-461.

Bray, G M, and A J Aguayo. 1974. "Regeneration of peripheral unmyelinated nerves. Fate of the axonal sprouts which develop after injury." *Journal of Anatomy* 117 (Pt 3) (July): 517-529.

Brück, W. 1997. "The role of macrophages in Wallerian degeneration." *Brain Pathology* 7 (2) (April): 741-752.

Brushart, T M. 1993. "Motor axons preferentially reinnervate motor pathways." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 13 (6) (June): 2730-2738.

Burant, C F, S K Lemmon, M K Treutelaar, and M G Buse. 1984. "Insulin resistance of denervated rat muscle: a model for impaired receptor-function coupling." *The American Journal of Physiology* 247 (5 Pt 1) (November): E657-666.

Cajal, S. 1928. *Degeneration and regeneration of the nervous system*. London: Oxford University Press.

Causey, G, and A A Barton. 1959. "The cellular content of the endoneurium of peripheral nerve." *Brain: A Journal of Neurology* 82 (December): 594-598.

Cotman, Carl. 1978. *Neuronal plasticity*. New York: Raven Press.

Cragg, B G, and P K Thomas. 1964. "The conduction velocity of regenerated peripheral nerve fibers." *The Journal of Physiology* 171 (May): 164-175.

Donaldson, D, O B Evans, and R W Harrison. 1986. "Insulin binding in denervated muscle." *Muscle & Nerve* 9 (3) (April): 211-215.

DuBois, D C, and S R Max. 1983. "Effect of denervation and reinnervation on oxidation of [6-14C]glucose by rat skeletal muscle homogenates." *Journal of Neurochemistry* 40 (3) (March): 727-733.

Dubový, P, and H Aldskogius. 1996. "Degeneration and regeneration of cutaneous sensory nerve formations." *Microscopy Research and Technique* 34 (4) (July 1): 362-375.

Duce, I R, and P Keen. 1980. "The formation of axonal sprouts in organ culture and their relationship to sprouting in vivo." *International Review of Cytology* 66: 211-256.

Ehlers, Michael D. 2004. "Deconstructing the axon: Wallerian degeneration and the ubiquitin-proteasome system." *Trends in Neurosciences* 27 (1) (January): 3-6.

Erez, Hadas, Guy Malkinson, Masha Prager-Khoutorsky, Chris I De Zeeuw, Casper C Hoogenraad, and Micha E Spira. 2007. "Formation of microtubule-based traps controls the sorting and concentration of vesicles to restricted sites of regenerating neurons after axotomy." *The Journal of Cell Biology* 176 (4) (February 12): 497-507.

Esper, Raymond M, and Jeffrey A Loeb. 2004. "Rapid axoglial signaling mediated by neuregulin and neurotrophic factors." *The Journal of Neuroscience* 24 (27) (July 7): 6218-6227.

Fawcett, J W, and R J Keynes. 1990. "Peripheral nerve regeneration." *Annual Review of Neuroscience* 13: 43-60.

Friede, R L, and R Bischhausen. 1980. "The fine structure of stumps of transected nerve fibers in subserial sections." *Journal of the Neurological Sciences* 44 (2-3) (January): 181-203.

Fu, S Y, and T Gordon. 1995. "Contributing factors to poor functional recovery after delayed nerve repair: prolonged denervation." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 15 (5 Pt 2) (May): 3886-3895. 1997. "The cellular and molecular basis of peripheral nerve regeneration." *Molecular Neurobiology* 14 (1-2) (April): 67-116.

Funakoshi, H, J Frisén, G Barbany, T Timmusk, O Zachrisson, V M Verge, and H Persson. 1993. "Differential expression of mRNAs for neurotrophins and their receptors after axotomy of the sciatic nerve." *The Journal of Cell Biology* 123 (2) (October): 455-465.

George, E B, J D Glass, and J W Griffin. 1995. "Axotomy-induced axonal degeneration is mediated by calcium influx through ion-specific channels." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 15 (10) (October): 6445-6452.

Geuna, Stefano, Stefania Raimondo, Giulia Ronchi, Federica Di Scipio, Pierluigi Tos, Krzysztof Czaja, and Michele Fornaro. 2009. "Chapter 3: Histology of the peripheral nerve and changes occurring during nerve regeneration." *International Review of Neurobiology* 87: 27-46.

Ghabriel, M N, and G Allt. 1977. "Regeneration of the node of Ranvier: a light and electron microscope study." *Acta Neuropathologica* 37 (2) (February 28): 153-163.

Goldberg, S, B Frank, and S Krayanek. 1983. "Axon end-bulb swellings and rapid retrograde degeneration after retinal lesions in young animals." *Experimental Neurology* 79 (3) (March): 753-762.

Gray, Henry. 1995. *Gray's anatomy : the anatomical basis of medicine and surgery.* 38th ed. New York: Churchill Livingstone.

Groves, M J, T Christopherson, B Giometto, and F Scaravilli. 1997. "Axotomy-induced apoptosis in adult rat primary sensory neurons." *Journal of Neurocytology* 26 (9) (September): 615-624.

Gulati, A K. 1988. "Evaluation of acellular and cellular nerve grafts in repair of rat peripheral nerve." *Journal of Neurosurgery* 68 (1) (January): 117-123.

Haftek, J, and P K Thomas. 1968. "Electron-microscope observations on the effects of localized crush injuries on the connective tissues of peripheral nerve." *Journal of Anatomy* 103 (Pt 2) (September): 233-243.

Hall, S M. 1986a. "Regeneration in cellular and acellular autografts in the peripheral nervous system." *Neuropathology and Applied Neurobiology* 12 (1) (February): 27-46. 1986b. "The effect of inhibiting Schwann cell mitosis on the re-innervation of acellular autografts in the peripheral nervous system of the mouse." *Neuropathology and Applied Neurobiology* 12 (4) (August): 401-414.

Hanz, Shlomit, and Mike Fainzilber. 2006. "Retrograde signaling in injured nerve--the axon reaction revisited." *Journal of Neurochemistry* 99 (1) (October): 13-19.

Heumann, R. 1987. "Regulation of the synthesis of nerve growth factor." *The Journal of Experimental Biology* 132 (September): 133-150.

Hoffman, P N, and D W Cleveland. 1988. "Neurofilament and tubulin expression recapitulates the developmental program during axonal regeneration: induction of a specific beta-tubulin isotype." *Proceedings of the National Academy of Sciences of the United States of America* 85 (12) (June): 4530-4533.

Hoffman, P N, D W Cleveland, J W Griffin, P W Landes, N J Cowan, and D L Price. 1987. "Neurofilament gene expression: a major determinant of axonal caliber." *Proceedings of the National Academy of Sciences of the United States of America* 84 (10) (May): 3472-3476.

Hoffman, S, D R Friedlander, C M Chuong, M Grumet, and G M Edelman. 1986. "Differential contributions of Ng-CAM and N-CAM to cell adhesion in different neural regions." *The Journal of Cell Biology* 103 (1) (July): 145-158.

Jander, S, and G Stoll. 1998. "Differential induction of interleukin-12, interleukin-18, and interleukin-1beta converting enzyme mRNA in experimental autoimmune

encephalomyelitis of the Lewis rat." *Journal of Neuroimmunology* 91 (1-2) (November 2): 93-99.

Jander, S, J Pohl, C Gillen, and G Stoll. 1996. "Differential expression of interleukin-10 mRNA in Wallerian degeneration and immune-mediated inflammation of the rat peripheral nervous system." *Journal of Neuroscience Research* 43 (2) (January 15): 254-259.

Jenq, C B, L L Jenq, and R E Coggeshall. 1987. "Numerical patterns of axon regeneration that follow sciatic nerve crush in the neonatal rat." *Experimental Neurology* 95 (2) (February): 492-499.

Kamber, Dotan, Hadas Erez, and Micha E Spira. 2009. "Local calcium-dependent mechanisms determine whether a cut axonal end assembles a retarded endbulb or competent growth cone." *Experimental Neurology* 219 (1) (September): 112-125.

Karns, L R, S C Ng, J A Freeman, and M C Fishman. 1987. "Cloning of complementary DNA for GAP-43, a neuronal growth-related protein." *Science* 236 (4801) (May 1): 597-600.

Koliatsos, V E, W L Price, C A Pardo, and D L Price. 1994. "Ventral root avulsion: an experimental model of death of adult motor neurons." *The Journal of Comparative Neurology* 342 (1) (April 1): 35-44.

Kreutzberg, G. W. 1995. *Reaction of the neuronal cell body to axonal damage.* S. G. Waxman, J. D. Kocsis, and P. K. Stys. The Axon: Structure, Function and Pathophysiology. New York: Oxford University Press.

Kubo, Tateki, Toshihide Yamashita, Atsushi Yamaguchi, Ko Hosokawa, and Masaya Tohyama. 2002. "Analysis of genes induced in peripheral nerve after axotomy using cDNA microarrays." *Journal of Neurochemistry* 82 (5) (September): 1129-1136.

Kurek, J B, L Austin, S S Cheema, P F Bartlett, and M Murphy. 1996. "Up-regulation of leukaemia inhibitory factor and interleukin-6 in transected sciatic nerve and muscle following denervation." *Neuromuscular Disorders* 6 (2) (March): 105-114.

LeBlanc, A C, and J F Poduslo. 1990. "Axonal modulation of myelin gene expression in the peripheral nerve." *Journal of Neuroscience Research* 26 (3) (July): 317-326.

Lindholm, D, R Heumann, M Meyer, and H Thoenen. 1987. "Interleukin-1 regulates synthesis of nerve growth factor in non-neuronal cells of rat sciatic nerve." *Nature* 330 (6149) (December 17): 658-659.

Liu, H M, L H Yang, and Y J Yang. 1995. "Schwann cell properties: 3. C-fos expression, bFGF production, phagocytosis and proliferation during Wallerian degeneration." *Journal of Neuropathology and Experimental Neurology* 54 (4) (July): 487-496.

Lubińska, L. 1982. "Patterns of Wallerian degeneration of myelinated fibres in short and long peripheral stumps and in isolated segments of rat phrenic nerve. Interpretation of the role of axoplasmic flow of the trophic factor." *Brain Research* 233 (2) (February 11): 227-240.

Lundborg, G, L B Dahlin, N Danielsen, H A Hansson, A Johannesson, F M Longo, and S Varon. 1982. "Nerve regeneration across an extended gap: a neurobiological view of nerve repair and the possible involvement of neuronotrophic factors." *The Journal of Hand Surgery* 7 (6) (November): 580-587.

Mackinnon, Susan. 1988. *Surgery of the peripheral nerve.* New York; Stuttgart; New York: Thieme Medical Publishers; G. Thieme Verlag.

Martin, L J, A Kaiser, and A C Price. 1999. "Motor neuron degeneration after sciatic nerve avulsion in adult rat evolves with oxidative stress and is apoptosis." *Journal of Neurobiology* 40 (2) (August): 185-201.

McQuarrie, I G. 1985. "Effect of conditioning lesion on axonal sprout formation at nodes of Ranvier." *The Journal of Comparative Neurology* 231 (2) (January 8): 239-249.

Meller, K. 1987. "Early structural changes in the axoplasmic cytoskeleton after axotomy studied by cryofixation." *Cell and Tissue Research* 250 (3) (December): 663-672.

Midrio, Menotti. 2006. "The denervated muscle: facts and hypotheses. A historical review." *European Journal of Applied Physiology* 98 (1) (September): 1-21.

Miller, F D, W Tetzlaff, M A Bisby, J W Fawcett, and R J Milner. 1989. "Rapid induction of the major embryonic alpha-tubulin mRNA, T alpha 1, during nerve regeneration in adult rats." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 9 (4) (April): 1452-1463.

Minwegen, P, and R L Friede. 1985. "A correlative study of internode proportions and sensitivity to procaine in regenerated frog sciatic nerves." *Experimental Neurology* 87 (1) (January): 147-164.

Mira, J C. 1984. "Effects of repeated denervation on muscle reinnervation." *Clinics in Plastic Surgery* 11 (1) (January): 31-38.

Molander, C, and H Aldskogius. 1992. "Directional specificity of regenerating primary sensory neurons after peripheral nerve crush or transection and epineurial suture A sequential double-labeling study in the rat." *Restorative Neurology and Neuroscience* 4 (5) (January 1): 339-344.

Myers, R R, H C Powell, M L Costello, P W Lampert, and B W Zweifach. 1978. "Endoneurial fluid pressure: direct measurement with micropipettes." *Brain Research* 148 (2) (June 16): 510-515.

Nathaniel, E J, and D C Pease. 1963. "Regenerative changes in rat dorsal roots following Wallerian degeneration." *Journal of Ultrastructure Research* 52 (December): 533-549.

Navarro, Xavier. 2009. "Chapter 27: Neural plasticity after nerve injury and regeneration." *International Review of Neurobiology* 87: 483-505.

Oblinger, M M, and R J Lasek. 1988. "Axotomy-induced alterations in the synthesis and transport of neurofilaments and microtubules in dorsal root ganglion cells." *The Journal of Neuroscience* 8 (5) (May): 1747-1758.

Perry, V H, M C Brown, and S Gordon. 1987. "The macrophage response to central and peripheral nerve injury. A possible role for macrophages in regeneration." *The Journal of Experimental Medicine* 165 (4) (April 1): 1218-1223.

Purves, D. 1975. "Functional and structural changes in mammalian sympathetic neurones following interruption of their axons." *The Journal of Physiology* 252 (2) (November): 429-463.

Rauvala, H, R Pihlaskari, J Laitinen, and J Merenmies. 1989. "Extracellular adhesive molecules in neurite growth." *Bioscience Reports* 9 (1) (February): 1-12.

Robinson, Grant A, and Roger D Madison. 2004. "Motor neurons can preferentially reinnervate cutaneous pathways." *Experimental Neurology* 190 (2) (December): 407-413.

Schlaepfer, W W. 1977. "Structural alterations of peripheral nerve induced by the calcium ionophore A23187." *Brain Research* 136 (1) (November 4): 1-9.

Schlaepfer, W W, and R P Bunge. 1973. "Effects of calcium ion concentration on the degeneration of amputated axons in tissue culture." *The Journal of Cell Biology* 59 (2 Pt 1) (November): 456-470.

Seddon, H. J. 1943. "Three types of nerve injury." *Brain* 66 (4) (December 1): 237 -288.

Seilheimer, B, and M Schachner. 1988. "Studies of adhesion molecules mediating interactions between cells of peripheral nervous system indicate a major role for L1 in mediating sensory neuron growth on Schwann cells in culture." *The Journal of Cell Biology* 107 (1) (July): 341-351.

Selander, D, and J Sjöstrand. 1978. "Longitudinal spread of intraneurally injected local anesthetics. An experimental study of the initial neural distribution following intraneural injections." *Acta Anaesthesiologica Scandinavica* 22 (6): 622-634.

Skene, J H, R D Jacobson, G J Snipes, C B McGuire, J J Norden, and J A Freeman. 1986. "A protein induced during nerve growth (GAP-43) is a major component of growth-cone membranes." *Science* 233 (4765) (August 15): 783-786.

Stoll, G, J W Griffin, C Y Li, and B D Trapp. 1989. "Wallerian degeneration in the peripheral nervous system: participation of both Schwann cells and macrophages in myelin degradation." *Journal of Neurocytology* 18 (5) (October): 671-683.

Sunderland, S, and K C Bradley. 1949. "The cross-sectional area of peripheral nerve trunks devoted to nerve fibers." *Brain: A Journal of Neurology* 72 (3) (September): 428-449.

Sunderland, Sydney. 1978. *Nerves and nerve injuries*. 2nd ed. Edinburgh; New York: Churchill Livingstone; distributed by Longman.

Thomas, P K, and D G Jones. 1967. "The cellular response to nerve injury. II. Regeneration of the perineurium after nerve section." *Journal of Anatomy* 101 (Pt 1) (January): 45-55.

Vanden Noven, S, N Wallace, D Muccio, A Turtz, and M J Pinter. 1993. "Adult spinal motoneurons remain viable despite prolonged absence of functional synaptic contact with muscle." *Experimental Neurology* 123 (1) (September): 147-156.

Vizoso, A D, and J Z Young. 1948. "Internode length and fibre diameter in developing and regenerating nerves." *Journal of Anatomy* 82 (Pt 1-2) (April): 110-134.1.

Waller, Augustus. 1850. "Experiments on the Section of the Glossopharyngeal and Hypoglossal Nerves of the Frog, and Observations of the Alterations Produced Thereby in the Structure of Their Primitive Fibres." *Philosophical Transactions of the Royal Society of London* 140 (January 1): 423-429.

Walsh, F S, and P Doherty. 1996. "Cell adhesion molecules and neuronal regeneration." *Current Opinion in Cell Biology* 8 (5) (October): 707-713.

Watts, Ryan J, Eric D Hoopfer, and Liqun Luo. 2003. "Axon pruning during Drosophila metamorphosis: evidence for local degeneration and requirement of the ubiquitin-proteasome system." *Neuron* 38 (6) (June 19): 871-885.

Waxman, Stephen. 1995. *The axon : structure, function and pathophysiology*. New York; Oxford: Oxford University Press.

Weinberg, H J, and P S Spencer. 1975. "Studies on the control of myelinogenesis. I. Myelination of regenerating axons after entry into a foreign unmyelinated nerve." *Journal of Neurocytology* 4 (4) (August): 395-418.

Witzel, Christian, Charles Rohde, and Thomas M Brushart. 2005. "Pathway sampling by regenerating peripheral axons." *The Journal of Comparative Neurology* 485 (3) (May 9): 183-190.

Ygge, J. 1989. "Neuronal loss in lumbar dorsal root ganglia after proximal compared to distal sciatic nerve resection: a quantitative study in the rat." *Brain Research* 478 (1) (January 23): 193-195.

Zhai, Qiwei, Jing Wang, Anna Kim, Qing Liu, Ryan Watts, Eric Hoopfer, Timothy Mitchison, Liqun Luo, and Zhigang He. 2003. "Involvement of the ubiquitin-proteasome system in the early stages of wallerian degeneration." *Neuron* 39 (2) (July 17): 217-225.
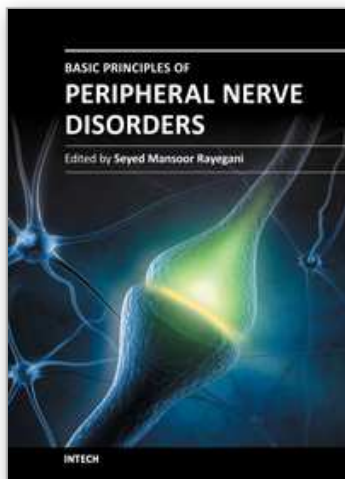
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Peripheral nerve disorders are comprising one of the major clinical topics in neuromusculoskeletal disorders. Sharp nerve injuries, chronic entrapment syndromes, and peripheral neuropathic processes can be classified in this common medical topic. Different aspects of these disorders including anatomy, physiology, pathophysiology, injury mechanisms, and different diagnostic and management methods need to be addressed when discussing this topic. The goal of preparing this book was to gather such pertinent chapters to cover these aspects.

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