Physiology of the Damaged Nerve

Peripheral nerve injuries are frequent and can cause serious disabilities. Their treatment sometimes leads to functional regeneration which often remains incomplete and random, despite the practice of rather sophisticated surgical techniques.

Two main classifications of peripheral nerve injuries have been established by Seddon and Sunderland (Figure 12). Seddon suggests a segmentation of injuries based on the residual function within the nerve. This classification distinguishes three degrees: neurapraxia, axonotmesis and neurotmesis. Sunderland adds two more degrees between axonotmesis and neurotmesis.

Pathophysiological Mechanisms

The most common causes of nerve injuries are traffic accidents, mostly those involving motorcycles. Statistically, peripheral nerve injuries are more frequent in the upper limbs (73.5% of traumatic injuries), particularly involving the ulnar nerve. The injury mechanisms most frequently implicated are traction, division, crushing and in a moderate way ischemia related with a compression on the peripheral nerve.

It seems important to insist on this type of damage in the sense that it is the one which characterises the genesis of entrapment neuropathy, regardless of which nerve is afflicted by compression.

A brief compression will stop nerve conduction and axonal transport, leading to a total motor and sensory paralysis (acute ischemia, followed by a regeneration occurring a few minutes later, e.g. the fibular nerve after keeping the legs crossed, numbness when waking up because of a compression of the median nerve at the brachial canal, etc.).

A chronic compression initially leads to a degeneration limited by the integrity of basal membranes. At the beginning, a distortion and an overlapping of the paranodal myelin emerge. Several layers of myelin can be involved, with a conduction slowdown. At the level of the affected segment, the myelin can retract itself in onion bulb formations and lead to a significant increase of endoneurial collagen. Ischemic phenomena coexist with a breakdown of the blood-nerve barrier (Figure 13). Prolonged compression leads to a degeneration of the distal nerve, with disuse atrophy, the paralysis happening in a belated way. The relieving of the compression will lead to a complete regeneration of the function if it happens before the denervation. The compression syndrome treatment efficiency illustrates this. The previous myelin is replaced and a proliferation of Schwann cells guarantees its reconstitution. Repeated cycles of demyelination and remyelination can follow and go so far as to coexist in neighbouring areas. The afflicted nerve segments show Schwann cells in an onion bulb shape and an increase in the density of the endoneurial interstitial tissue by proliferation of the collagen. The continuity of basal membranes allows for functional regeneration for a long time after treatment.

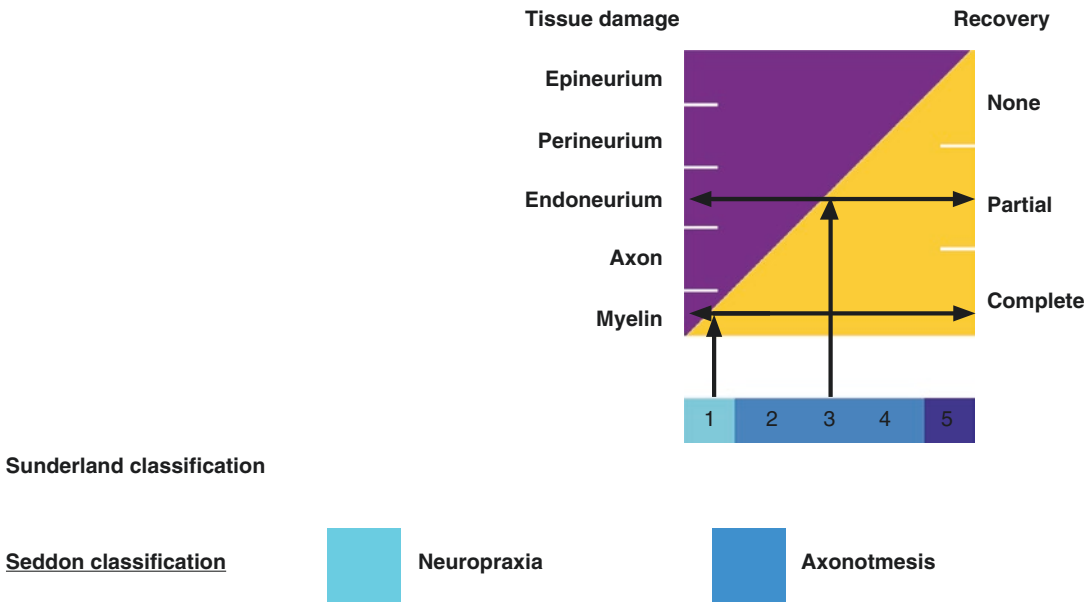
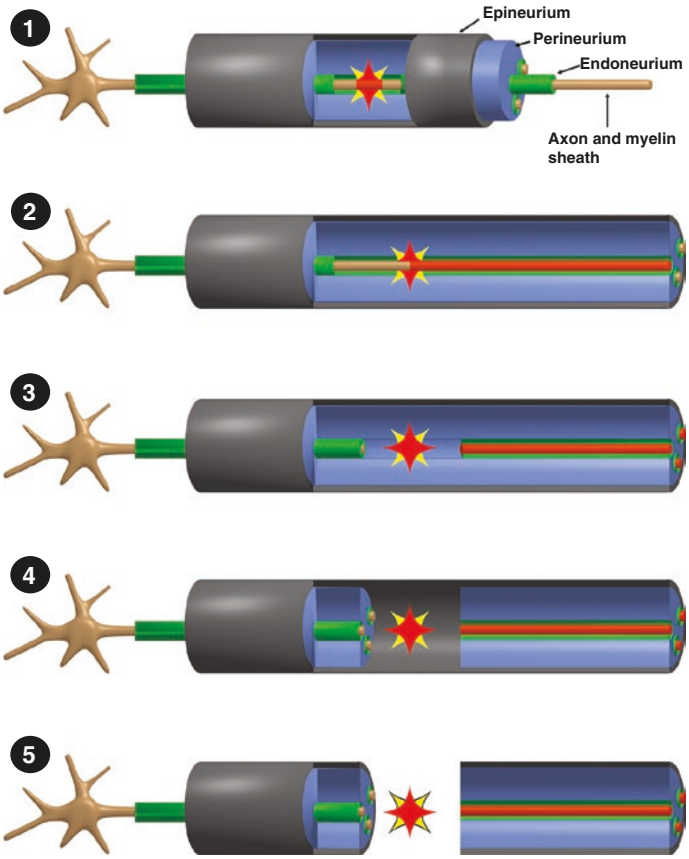


Figure 12. Diagram of recovery according to the level of tissue injury (According to Seddon [3] and Sunderland [4])



1. Description of the axon
2. Isolated axonal injury
3. Axon injury of the myelin sheath and of the endoneurium
4. Axon injury of the myelin sheath, the endoneurium and of the perineurium
5. Injury of all the nerve structures

Figure 13. Various types of axon injury structure

Nerve Degeneration

In cases of acute nerve damage or chronic compressions without division of the axonal continuity (injuries of the first degree), we find some modifications of the myelin sheath starting with a contusion extending up to the concerned paranodal area (Figure 14). It can extend over a few adjacent segments and cause a decrease in conduction speed. In acute cases, one can observe conduction blocks even though an electrophysiological test of each of the nerve's extremities remains normal. There is a regenerative process that leads to a remyelination after an elimination of the damaged myelin. In chronic compressions, successive demyelination-remyelination cycles lead to the formation of a segmental onion bulb-shaped morphology linked to the proliferation of Schwann cells and to the expansion of the interstitial endoneurial content invaded by collagenic material. In second-degree and above injuries, there are visible changes at the level of the injury's area, but it is mostly the distal segment that will suffer a process of anterograde degradation called Wallerian degeneration, according to a chain of events whose initial trigger is calcium dependent. The first modifications lead to a myelinic and axonal fragmentation and start in the first hours after the trauma. It takes place with the same kinetics as the Wallerian anterograde degeneration, namely, a retrograde degeneration. It generally only affects some segments with an identical lesional sequence (Figure 15).

The degeneration reaches its peak after a division of the nerve containing in and of itself an interruption of the basal membranes and a functional failure of the emitting function of the neuron, the somatodendritic ramifications being the receiving function. The peripheral nerve's reaction is unique, which differentiates it from the constituting elements of the central nervous system. The existence of initiated compensating mechanisms within the motor neurons during pathological or traumatic processes is accepted without doubt nowadays [5, 6]. It has thus been demonstrated that after axonal injuries, the peripheral nervous system's neurons were able to regenerate their axons to reinnervate various targets [7].

A : Diagram of a nerve under physiological conditions

B : Diagram of a possible traumatic injury

1. Healthy neuron
2. Myelin sheath
3. Axon
4. Cell nucleus
5. Injured myelin before phagocytosis
6. Injured myelin
7. Wallerian degeneration of the axonal swelling
8. Soma
9. Macrophage

A : About 24 hours after injury. Wallerian degeneration of the distal part of the peripheral nerve. First signs of chromatolysis.

B : 10 to 21 days after injury. First signs of denervation atrophy of the target muscle fibres. Band of Bungner along the proliferating Schwann cells. Formation of axonal growth cone at the level of the proximal swelling. Visible chromatolysis.

C : Several months after injury. Extensions of axonal sprouting growing at various speeds, among which one or several extend within the band of Bungner, but haven't reached their target. Advanced stage of muscle denervation. Regression of the chromatolysis reactions in the soma.

D : Reinnervation of the target organ by the faster-growing axons. The motor end plate becomes functional again and conduction is restored. Regression of the other extensions. Progressive remyelination. The muscle fibres recover a subnormal thickness.

E : Formation of a neuroma. The muscle fibres that were denervated for more than a year destructure and are subject to an important interstitial fibrosis.

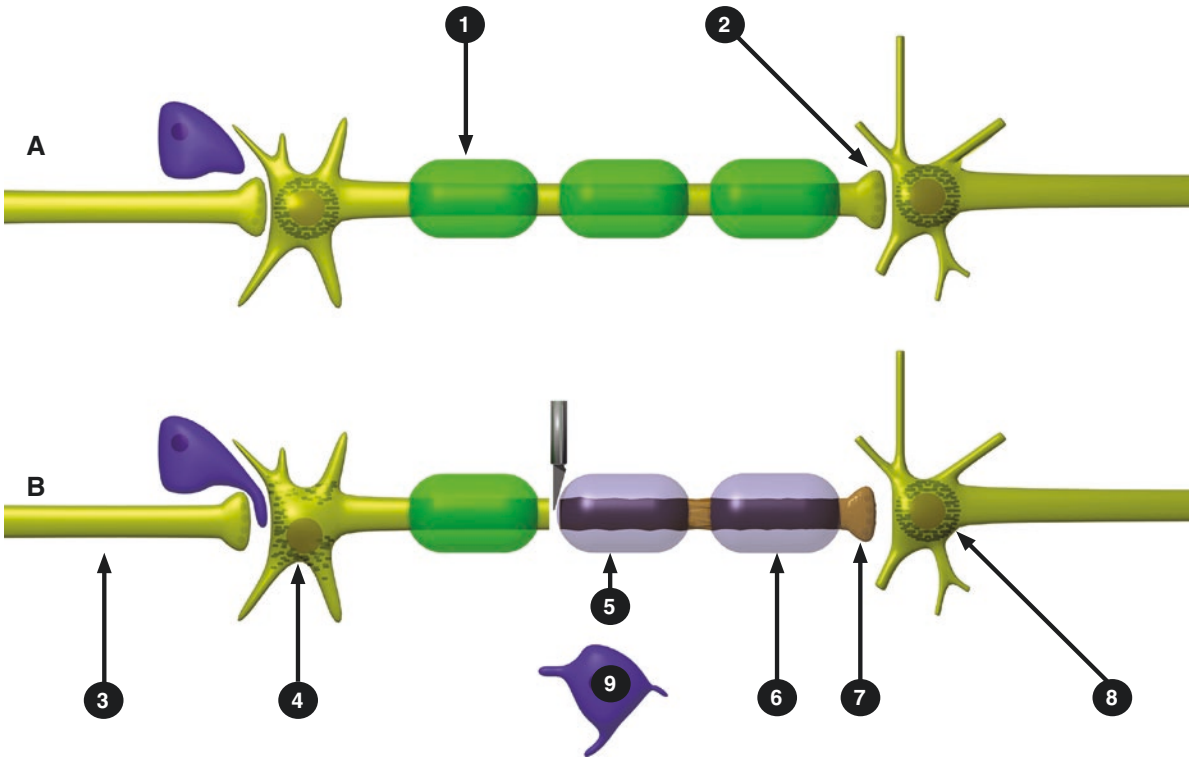


Figure 14. Traumatic injury of an axon (According to Keirstead et al. (1999))

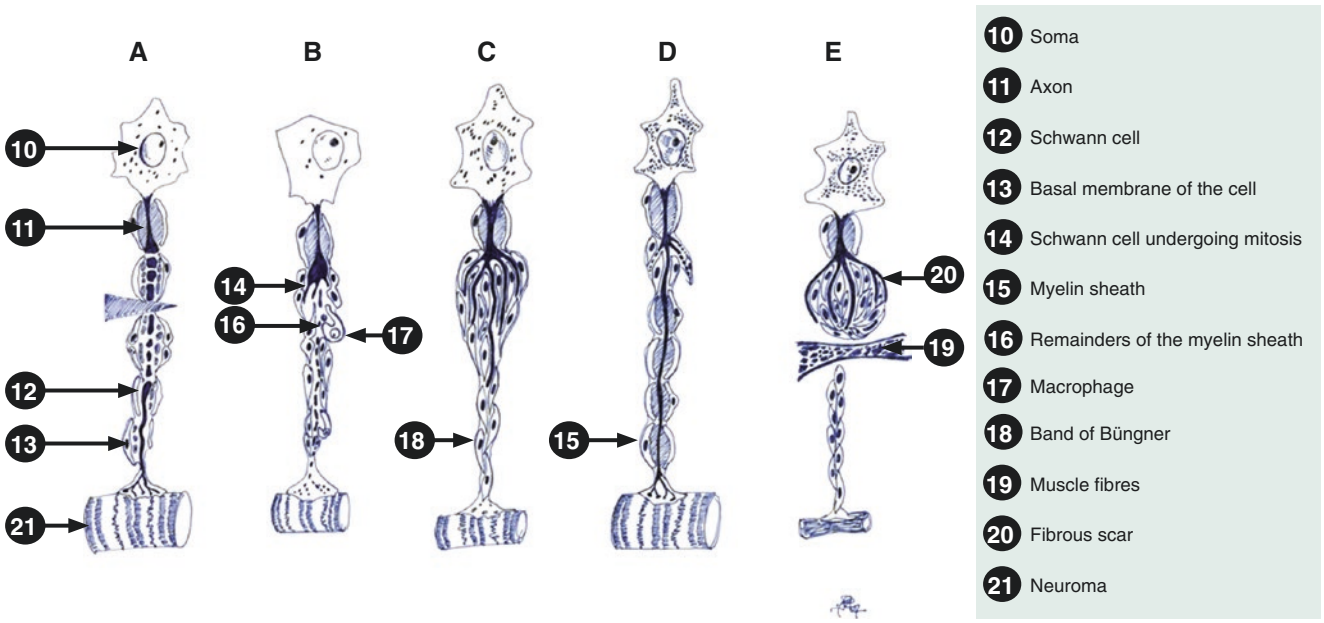


Figure 15. Various types of axon degeneration

Mechanisms of Neural Repair

In acute trauma, regeneration only begins at the end of the Wallerian degeneration phase, whilst in moderate injuries the process begins nearly immediately. A chain of events follow the trauma, involving neurotrophic factors and cell signalling molecules. Schwann cells have an essential role: firstly, by intensifying the synthesis of adhesion molecules to their surface and by favouring the growth of extracellular protein matrix and, secondly, by activating certain genes by means of neurotrophic factors linking themselves to tyrosine kinase receptors.

Axonal Sprouting

When an injury afflicts the peripheral nerve, an axon sprouts back from the proximal segment towards the currently degenerating distal fragment, colonising it by tunnelling in order to reach the synapse again and this way form a new nerve termination. Thus, motor neurons can not only constitute a new NMJ but also synapses of the three types of the PNS axons (motor, sensory and autonomous system).

The main mechanism involved is represented by axonal sprouting. It allows surviving motor neurons to increase the size of their motor unit (MU) (including the motor neuron and all the muscle fibres innervated by it), reinnervating the denervated muscle fibres to reach several times the size of a normal MU [8–15]. However, when there is only 20% functional MU, the expanding capacity of the MU is insufficient to reinnervate all the denervated muscle fibres: an amyotrophy then takes place.

Axonal sprouting allows for the apparition of thin axonal ramifications coming from healthy axons. It starts at the level of the proximal extremity of damaged fibres, generally in the first hours after the trauma, but sometimes there can be several days before the cellular prolongation appears from the damaged proximal extremity. A growth cone forms at the extremity of the regenerating axon. It is a specialised apparatus, with motility abilities, endowed with "exploration" properties. The scar tissue's characteristics at the level of the damaged area, if unfavourable, can prevent the axon from reaching the distal extremity, getting lost in the conjunctive tissue and growing chaotically to form a neuroma in the region of the proximal stump. Some axons can nevertheless get through the scar, forming a neuroma called "neuroma-in-continuity".

Three categories of axonal sprouting are defined according to their function at the level of the emerging sprout: the "ultra-terminal" sprouting which guides the axonal sprout towards the NMJs (Figure 16a) with a base emerging from the main axon just before its blooming in the synapses, the preterminal sprouting taking its source more distantly from the axonal termination (Figure 16b) and the nodal sprouting at the level of the nodes of Ranvier (Figure 16c). An intense axonal germination becomes necessary when more than 85% of the motor neurons have been destroyed and remains random when only 20% of these have subsisted. In extreme cases, a single axon can then emit several types of sprouting (Figure 16d), or even several sprouts of the same type (Figure 16e). The capacity of motor neurons to increase the number of muscle fibres within their MU, thanks to axonal sprouting by a factor of three to eight, was demonstrated by electrophysiological tests [8–11]. Furthermore, it has been demonstrated that even though there is a diminution of the number of MU during denervations, the remaining MUs are compensated by an increase of contractility proportional to the degree of denervation.

Axonal sprouting is a crucial parameter to consider when trying to understand the pathophysiological mechanisms that are responsible for motor neuron loss, but also in clinical implications that it can create in the context of various pathologies such as polymyelitis, amyotrophic lateral sclerosis, partial nerve injuries or even functional denervations.

Despite the attempts of motor compensation involved in these pathologies, it has been clearly demonstrated that an absence of activity, or on the contrary a neuromuscular activity that is too intense, was harmful to axonal sprouting in the patient's partially denervated muscles.

The understanding of these mechanisms at the base of these contradictory effects has led more recently to a suggestion of reeducation strategies for patients based on moderate muscular mobilisations, favouring axonal sprouting and optimising perhaps a potential functional regeneration.

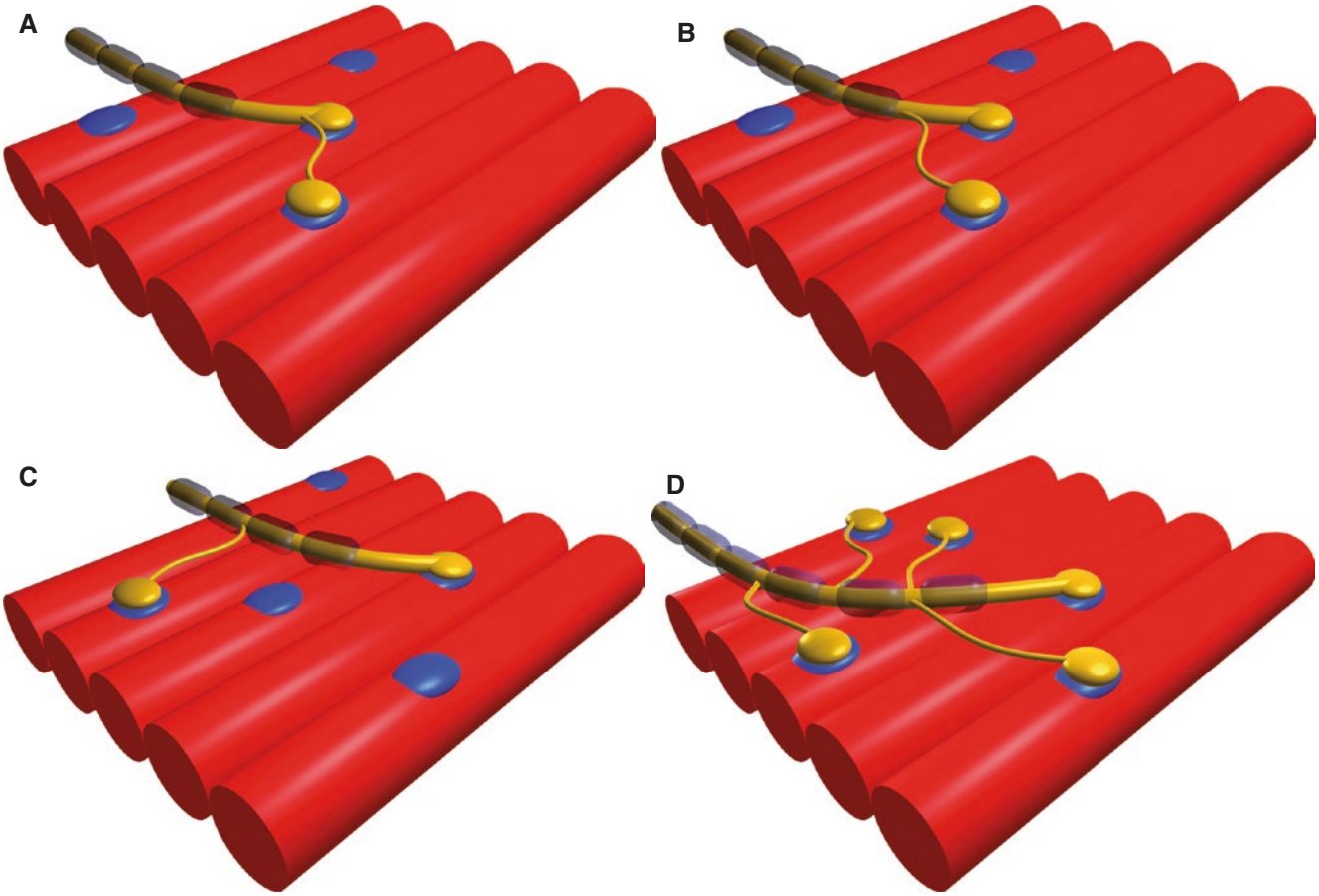


Figure 16. Axonal sprouting (According to Tam et al. [13])

A : Extension coming from the main axon before expansion into the synaptic gutters

B : Preterminal Sprouting emerging remotely from the axonal terminal

C : Nodal sprouting in relation to the nodes of Ranvier

D : One axon can therefore emit several types of sproutings

Neurotrophic Factors

The smooth progress of degeneration/regeneration processes requires a sophisticated cellular communication system, triggering complex cellular signalisation spates, as well as an elaborate trophic and tropic system, similar to those of the inflammatory processes. Factors such as the NGF (neurotrophic growth factor) or BDNF (brain-derived neurotrophic factor) and many others have been identified and participate to its cellular survival and sustenance in normal conditions. NGF, for example, is modulated in an extremely dynamic way by the target of the peripheral nerve and then transported at the soma's level by the retrograde axonal flow. Its concentration at the soma's level diminishes during an injury. It could be the molecular factor triggering regeneration processes. These neurotrophic factors are linked to specific receptors that transmit the cell signalisation and regulate the activation of many genes. For instance, we can find these receptors on Schwann cells forming bands of Bungner, the concentration of which increases after an injury. They are themselves subjected to complex regulation mechanisms. NGF is also found in the growth cone and transmitted to the soma in a retrograde way, thus continually stimulating axonal growth, as well as guiding it by an interaction with Schwann cells.

Potential Functional Consequences

Axonal regeneration doesn't imply a functional *restitutio ad integrum*. It ends with a maturation process within the new axon at a lower speed than its first growth phase and can last up to a year. Remyelination follows a similar scenario to the one observed during the development leading to an alignment of Schwann cells that wrap around each axon of a myelin sheath with multiple layers. It begins within 2 weeks after axonal regeneration.

Functional Regeneration

It doesn't necessarily need a perfect regeneration of the nerve's architecture. However, the effects of a prolonged denervation, significantly altering the functional regeneration, are proportional to its evolution period. They are linked to nerve regeneration difficulties but also to the modifications of the target at the peripheral and central levels (neuroplasticity). The key factor of nerve regeneration is the conservation of basal membranes. Even in the case of significant motor regeneration, the functional result is hampered by concomitant sensory deficiencies, especially proprioceptive. Sensory receptors can persist after a year and allow functional reconnections. The sensory scheme is relatively well conserved in first- and second-degree injuries, thanks to the connections from the correct axons to correct receptors. After more acute injuries and nerve regeneration, sensory regeneration is always incomplete. Finally, let's highlight the very poor possibility of regeneration of vegetative fibres. Many factors participate to this phenomenon: notably the impossibility for some axons to gain their receptors back, the existence of crossed reinnervations, and a possible degradation of some receptors, or some cortical modifications linked to neuroplasticity.

Neuroplasticity

Peripheral nerve injuries and their regeneration cause functional modifications of the corresponding cortical areas. These modifications can be found at the level of the thalamic projections, the brain stems and probably at the medullary level following a sequence that remains unknown. This phenomenon is a part of cerebral plasticity. The recovery will be complete if the denervated area is minor or limited and if it is wider, with silent residual cortical areas. The end of these substitution and reorganisation cycles is divided into two phases: a precocious first phase of quick reactivation within a few hours and then a second, slower phase. The same mechanisms can be observed on the motor facet. In peripheral nerve injuries, there are sensory modifications caused by cortical modifications: irrational sensations due to substitutions of impulses and over-representation of adjacent areas generating hyperpathia, troubles of localisation, astereognosis and hypersensibility (hyperesthesia, hyperpathia, dysesthesia). Phantom limb pain finds some of its anatomical substrate in these rearrangements. The peripheral nerve's regeneration, incomplete, will once again disturb this organisation. The taking over of these projection areas will generally remain incomplete, even after a long evolution period. It is more often than not chaotic, in patches; some reinnervated areas can have several representations or none at all. These representations can be misplaced. The last reorganisation leads to a cortical representation that is smaller and disharmonious, conserving patches of representation in adjacent areas. This territorial compromise is the source of dysfunctions.

Conclusion

The peripheral nerve's reaction to an injury is unique and differs from the one encountered at the level of the central nervous system. It takes place according to a complex process of degeneration and regeneration that remains to this day only partially elucidated. The molecular and cellular biology's progresses bring additional hope towards future therapeutic and medico-surgical advances in taking charge of peripheral nerve injuries, optimising the already astounding abilities of spontaneous regeneration. Perhaps they will also allow researchers to better understand why the central nervous system doesn't possess such properties and bring stimulation and regeneration strategies in the neuraxis as well as in the peripheral nervous system.

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