Summary. Recovery from peripheral nerve injury depends on a variety of factors, both intrinsic and extrinsic to neurons. Wallerian degeneration, neuronal reaction, axonal growth and target reinnervation are sequential processes that occur after a peripheral nerve injury. The capability of severed axons to regenerate and recover functional connections is dependent on the site and type of lesion, and the distance over which axons must re-grow to span the injury. The management of most nerve injuries is presently limited to surgical repair, by direct suture of the stumps or by interposition of a nerve graft to provide axons growing from the proximal stump with a substrate supporting regeneration. The development of artificial nerve grafts, composed of a guide filled with molecular and cellular elements that promote axonal regeneration is a strategy to facilitate regeneration and to solve the secondary problems of autograft and allograft repair.

1. INTRODUCTION

The peripheral nervous system is constituted by groups of neurons whose cell bodies are located in the spinal cord or within spinal ganglia, their intrinsic central connections, and their axons, which extend through peripheral nerves to reach target organs. Functionally, the peripheral nerves contain several types of nerve fibers. Afferent sensory fibers can be unmyelinated or myelinated (the latter ranging from 2 to 20 μm in diameter) and terminate at the periphery either as free endings or in a variety of specialized sensory receptors in the skin and deep tissues. Efferent motor fibers originate from motoneurons in the anterior horn of the spinal cord and end in neuromuscular junctions in skeletal muscles; the majority can be divided into two types: alpha-motor fibers, with diameters between 10 and 17 μm, which synapse with skeletal muscle fibers, and gamma-motor fibers, 3 to 8 μm in diameter, innervating muscle spindles. Efferent autonomic fibers in somatic peripheral nerves are constituted by postganglionic sympathetic fibers, generally unmyelinated, which innervate smooth muscle and glandular structures. The number and type of nerve fibers vary markedly depending on the nerve and the anatomical location. In somatic nerves, such as those of the limbs, the number of unmyelinated fibers is approximately twice that of myelinated ones. Most peripheral nerves are mixed, providing motor, sensory, and autonomic innervation to the corresponding projection territory.
Nerve fibers, both afferent and efferent, are grouped in fascicles surrounded by connective tissue in the peripheral nerve. The fascicular architecture of a peripheral nerve changes throughout its length, with a higher number of smaller fascicles in distal than in proximal segments. In addition to bundles of nerve fibers, the peripheral nerves are composed of three supportive sheaths: epineurium, perineurium and endoneurium. The epineurium is the outermost layer, continuous with the mesoneurium and the connective sheaths of surrounding tissues. It is a loose connective tissue and carries the blood vessels that supply the nerve. The perineurium is the sheath surrounding each fascicle in the nerve. It consists of inner layers of flat perineurial cells and an outer layer of collagen fibers organized in longitudinal, circumferential, and oblique bundles. The perineurium contains a blood vessel network connected with epineurial vessels and with endoneurial capillaries. The perineurium is the main contributor to the tensile strength of the nerve, acts as a diffusion barrier and maintains the endoneurial fluid pressure. The endoneurium is composed of fibroblasts, collagen and reticular fibers, and extracellular matrix, occupying the space between nerve fibers within the fascicles. The endoneurial collagen fibrils are packed around each nerve fiber to form the walls of the endoneurial tubules. Inside these tubules, axons are accompanied by Schwann cells, which either myelinate or just surround the axons. The basal laminae produced by Schwann cells are arranged in continuous tubes around the axon/Schwann-cell units.

Following injuries to peripheral nerves, the motor, sensory, and autonomic functions conveyed by the involved nerves will be partially or totally lost in the denervated segments of the body, due to the interruption of axon continuity, degeneration of nerve fibers distal to the lesion and eventual death of axotomized neurons. These deficits can be compensated by reinnervation of denervated targets following two compensatory mechanisms: regeneration of injured axons and collateral branching of undamaged axons in the vicinity. However, clinical and experimental evidence usually shows that these mechanisms do not enable for a satisfactory functional recovery, especially after severe injuries.

2. NERVE INJURIES

2.1. Classification of nerve injuries

Axonal damage by crush, transection, ischemia, or inflammation leads to interruption of axonal continuity with ensuing degeneration of nerve fibers distal to the lesion site. The nerve trunk injured, and the type and severity of the lesion, determine the need for surgical repair and the technique to apply. The prognosis for functional return is correlated with the degree of intraneural disruption. This is why the most popular classifications of mechanical nerve lesions (those of Seddon and of Sunderland) are based upon the morphology of the lesion and the nerve sheaths damaged. The most detailed classification, that of Sunderland, differentiates five degrees of injury. The first degree (neurapraxia of Seddon) corresponds to focal blocking of impulse conduction, usually due to compression. Large nerve fibers are more readily damaged than small ones. Histologically there is damage of the myelin