EXPERIMENTAL STUDY ON THE DIFFERENT METHODS FOR TREATMENT OF PERIPHERAL NERVE INJURY

THESIS

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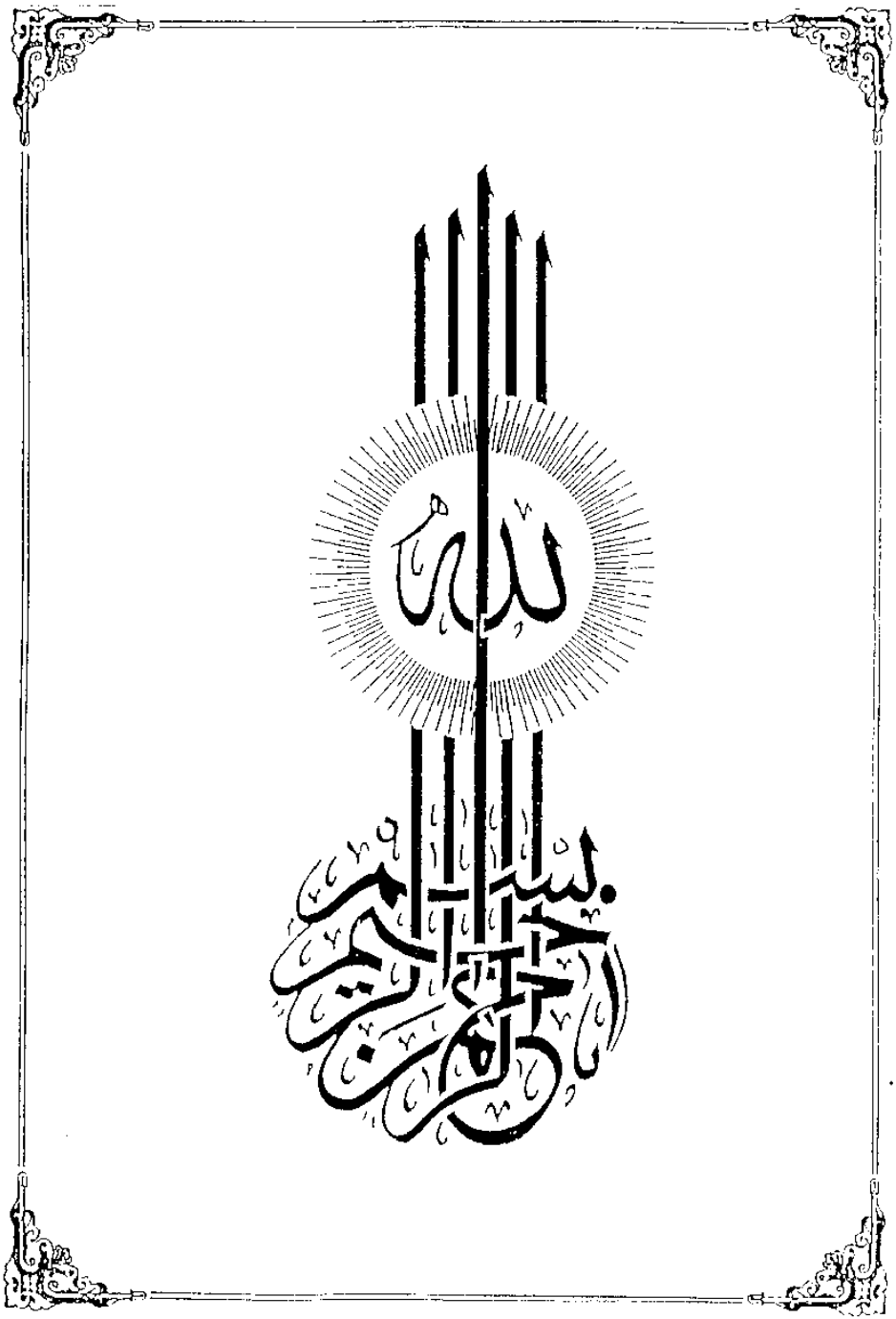

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Introduction

INTRODUCTION

Although the ability of peripheral nerve to regenerate following injury is well known (*Gutman*, 1942 and *Mcloon and La Velle*, 1981); the basic mechanisms and factors controlling nerve regeneration are a mystery (*Seckel et al.*, 1984).

With the introduction of the operating microscope, together with fine instruments and suture materials, the results of peripheral nerve repairs have been improved (*Tupper et al.*, 1988). But in spite of this improvement, the clinical results of surgical nerve repair are still disappointing (*Millesi*, 1981a).

One basic problem with peripheral nerve regeneration following complete nerve transection or separation between the nerve ends is the creation of a gap (*Frykman and Cally*, 1988).

Many surgeons prefer to treat peripheral nerve injuries with a gap by nerve grafting rather than suturing the nerve under tension (*Millesi et al.*, 1972b; *Millesi et al.*, 1976; *Miyamoto et al.*, 1979 and *Miyamoto*, 1979). Nerve suturing and grafting; which were derived from the idea that direct proximal-to-distal nerve suture is essential for successful nerve regeneration; were based on theories developed long ago (*Seckel et al.*, 1984), by some physiological investigators as those of Cruickshank and

Haighton in the end of the 18th century and by Waller's studies in 1850 (After *Seckel et al.*, 1984).

During most of the 100 years following Waller's studies on the degenerative changes that occur in the distal nerve stump following transection of a peripheral nerve, his concept of the importance of the nerve cell body as a trophic or nutritive center that supports the distal nerve's existence, function and regenerative capabilities was preeminent in neurobiological thought.

Although some authors (*Harrison*, 1910 and *Hamburger*, 1934) early in this century postulated that factors in the periphery exerted important effects on centrally situated nerve cells; convincing evidence of this modern concept awaited the end of world war II. The discovery of the nerve growth factor (NGF) by Levi-Montalcini and Hamburger, in 1951, and its subsequent purification by Cohen, in 1954, truly revolutionized the study of the biology of nerve regeneration leading to the discovery of many target-derived neuron trophic factors (TDNTF). On the basis of these recent theories, the concept of bridging a gap between nerve ends with a non-neural conduit had evolved, with a considerable interest (*Seckel et al.*, 1986).

It is difficult to perform well controlled clinical studies in humans because of difficulties in obtaining sufficient numbers of patients with peripheral nerve injuries who all match for age, location, mechanisms of

injury, severity of injury, and other associated injuries. In contrast to clinical studies, animal studies provide the investigator with much greater control over the variables of nerve regeneration and have the opportunity to develop animal models to study each variable independently (*Frykman et al., 1988*).

It is well known that dogs had travelled to space prior to man. So, human beings have to be grateful to animals because they are taking the risk for improving our knowledge for a safer application in humans, to a great extent, with better results.

In spite of the different methods for treating peripheral nerve injury based on old and recent theories of nerve regeneration and utilizing modern techniques and fine instrumentation, the results of these different methods have generated as many questions as they answered (as often happens in science).

It is hoped that this work will answer little and generate many questions for the future researchers and to be a step in driving back the peripheral nerve injuries to its natural home, the field of neurosurgery.

Review of Literature

MORPHOLOGICAL BASIS OF THE PERIPHERAL NERVES

The peripheral nervous system is all those parts of sensory, lower motor and autonomic neurons that lie outside the confines of the central nervous system (*Bennington*, 1978). It represents a composite tissue constructed for the purpose of maintaining continuity, nutrition and protection of its basic functional elements – the nerve fibres (*Lundborg*, 1988a). So, the peripheral nerve consists of both neural (nerve fibre) and non-neural (connective tissue) elements (*Neumann*, 1988). Connective tissue elements include the epineurium, perineurium and endoneurium (*Chiu and Ishii*, 1986) (Fig. 1).

The Nerve Fibre

Nerve fibres can be divided into myelinated and non-myelinated. In the myelinated fibre one axon is associated with only one Schwann cell. The membrane of the Schwann cell being wrapped spirally around the axon producing a sheath of alternating layers of lipid and protein: the myelin sheath. In non-myelinated fibres, one Schwann cell accumulates a great number of axons (*Lundborg*, 1988a). (Fig. 1). The junction between the myelin sheaths of two adjacent Schwann cells represents the node of Ranvier (*Bennington*, 1978).

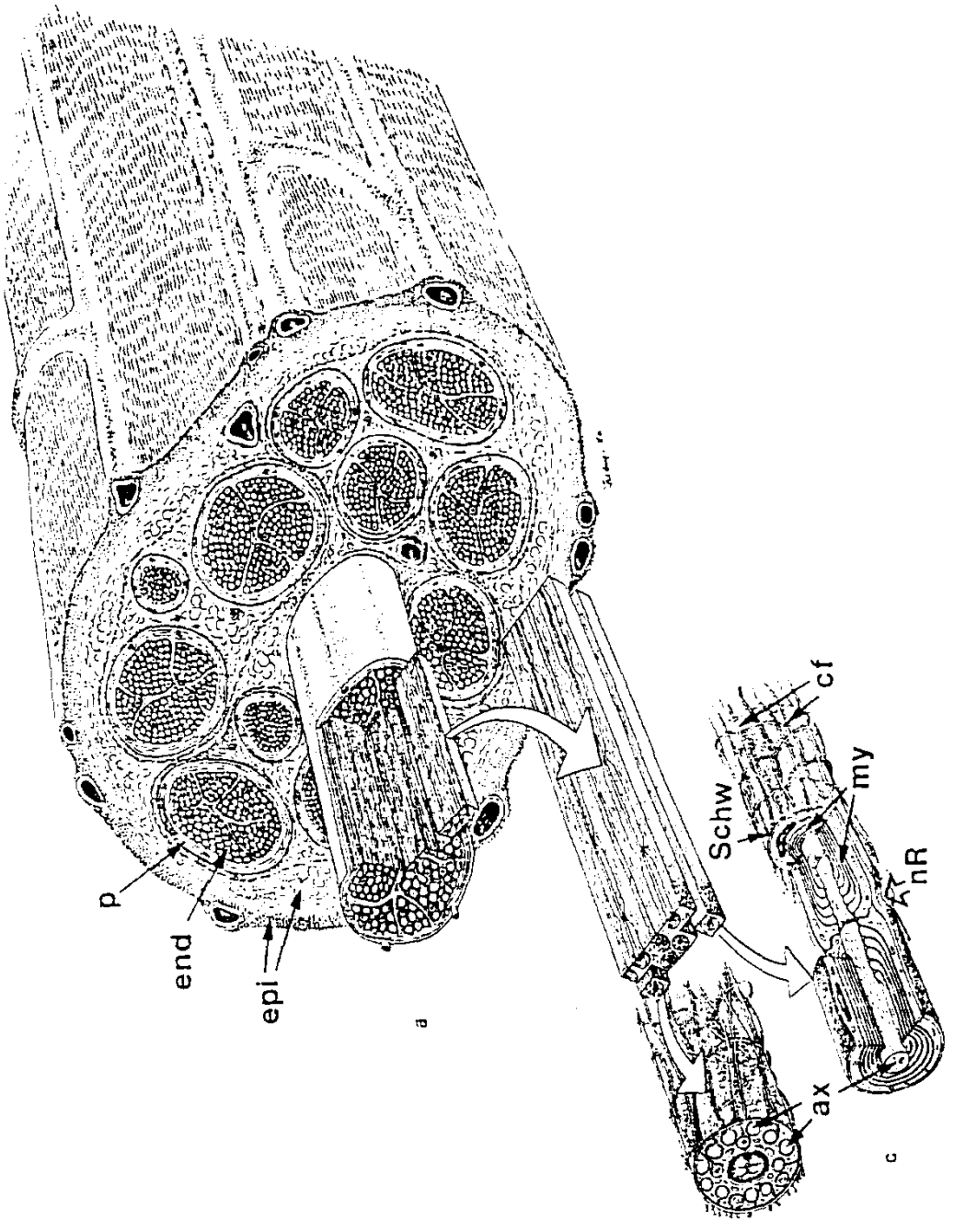

Fig. (1): Microanatomy of a peripheral nerve trunk and its components. a) Fascicles surrounded by a multilaminated perineurium (p) are embedded in a loose connective tissue, the epineurium (epi). The outer layers of the epineurium are condensed into a sheath. b) and c) illustrate the appearance of unmyelinated and myelinated fibres respectively. Schw: Schwann cell; my: myelin sheath; ax: axon; nR: node of Ranvier.

(*Lundborg*, 1988a)

Myelinated fibres vary in outside diameter from 1–20 microns, and there is a direct relationship between axon caliber and thickness of myelin sheath; (larger fibres having thicker sheaths). Also, the nerve conduction velocity is related to nerve fibre size (the largest fibres conducting the fastest). The nerve conduction studies determine the maximum velocity for a given nerve, and therefore assess the function of only the largest myelinated fibres that can be excited (*Bennington*, 1978).

Classification of Nerve Fibres

Depending on the direct proportional relationship between total fibre diameter and conduction velocity (*Rushton*, 1951) various groups have been made on the basis of size and conduction velocity (*Lundborg*, 1988a).

Group A (Diameter 5–20 μm)

It includes the largest fibres with the fastest conduction velocity. It is subdivided by fibre size into:

- Aα (diameter 15–20 μm): It represents the efferent motor fibres.
- Aβ (diameter 8–15 μm): It is associated with touch.
- Aγ (diameter 2–8 μm): It is concerned with sharp pricking pain and temperature.

Group B (Diameter 1–2 μm)

It contains the myelinated autonomic and preganglionic fibres.

Group C (Diameter 0.1–1 μm)

Burning pain has been referred to this thin, unmyelinated group.

The Connective Tissue

1. The Endoneurium

The term endoneurium specifies the delicate connective tissue stroma and fibroblasts that lie in septa and between individual nerve fibres within fascicles (*Bennington*, 1978) (Fig. 1).

2. The Perineurium

The term perineurium indicates the circulatory arranged tissue that invests each fascicle (*Bennington*, 1978). The perineurium forms a dense, mechanically strong sheath, surrounding each fascicle and acting as a mechanical barrier to external trauma. It also serves as a diffusion barrier. The barrier function makes the perineurium an important structure for preservation of the specific internal environment of the endoneurium (*Kristensson and Olsson*, 1971; *Olsson and Kristensson*, 1971, 1973 and *Thomas and Olsson*, 1984). The mechanical strength of the perineurium is impressive. The intrafascicular pressure can be experimentally raised to 300–750 mmHg before rupture of the perineurial membrane occurs (*Selander and Sjöstrand*, 1978).

The Perineurium as a Diffusion Barrier

From the numerous studies, involving the use of various tracer techniques, it is apparent that the perineurium constitutes a diffusion barrier to various externally applied substances such as ferritin (*Waggener et al.*, 1965 and *Oldfors*, 1981), small molecule proteins (*Olsson and Reese*, 1969, 1971; *Soderfeldt et al.*, 1973, *Oldfors and Sourander*, 1978 and *Oldfors and Johansson*, 1979) and to exogenous proteins (*Lundborg*, 1970; *Olsson et al.*, 1971; *Lundborg et al.*, 1973 and *Soderfeldt et al.*, 1973).

The barrier function works from inside outwards as well as from outside inwards (*Lundborg*, 1973). It is confined to the innermost layers of the perineurial lamellae (*Lundborg*, 1988b).

Together with the diffusion barrier constituted by the walls of the endoneurial capillaries (the blood nerve barrier) the perineurium protects the endoneurium from external influences, providing an effective filter action against the influx of ions, proteins and other potentially hazardous agents. For instance, it has been observed that peripheral nerves can pass through pyogenic foci without nerve function being in any way influenced – a fact probably due to the perineurial barrier function (*Lundborg*, 1988b). This special endoneurial environment is believed to be of the utmost importance for optimal nerve fibre function – a

suggestion which is supported by the impaired nerve function seen in association with experimental barrier damage (*Lundborg*, 1970, 1975).

The perineurial barrier is remarkably resistant to mechanical trauma, a fact which is important in several surgical procedures. Although the barrier is damaged by pinching a nerve with a pair of forceps (*Soderfeldt et al.*, 1973), the barrier action is not necessarily damaged when intraneural dissection for instance internal neurolysis, is performed (*Rydevik et al.*, 1976). Such a procedure induces a severe epineurial oedema. The perineurial barrier is important in protecting the nerve fibres from associated damage (*Lundborg*, 1988b).

The perineurial barrier function has also proved markedly resistant to compression trauma: its permeability to externally applied protein molecules does not increase even under local external compression of 400–600 mmHg for 2 hours (*Rydevik and Lundborg*, 1977). However, local crush injury induced in the peripheral nerves of experimental animals results in abnormal permeability of the perineurium at the site of trauma, persisting for at least 4 months. This opening of the perineurial filter is also disadvantageous for other parts of the nerve, since the substances gaining entrance to the endoneurial space at the site of trauma may spread over wide distances inside the corresponding fascicle, mainly distally (*Olsson and Kristensson*, 1973).

The perineurial barrier is remarkably resistant to ischaemia; in experimental animals as well as in humans. The barrier function is still