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PAST, PRESENT, AND FUTURE OF NERVE REPAIR

A written description of the peripheral nervous system was recorded by Hippocrates as early as the 4th century B.C.,¹ and by Herophilus in the 3rd century B.C., who identified nerves as such, distinguished them from tendons, also traced nerves to the spinal cord, and separated them into motor and sensory components.² The traditional Hippocratic teaching of the time, however, doubted that nerve healing occurred.

Regarding the repair of severed nerves, history is silent until Galen of Pergamon (131–201 A.D.),³ who was the first to study the effects of transections of peripheral nerves, and who reported incredible results where severed nerves had been sutured. Nothing in his writings suggested that he, himself, ever used the procedure.

Although there is reference to nerve suture by Paul of Aegina (625–690 A.D.),² the first clear reference to the suture repair of a severed nerve is attributed to the Persians, Rhazes (850–932) and Avicenna (980–1037).² During the Middle Ages, suture of severed nerves was only briefly mentioned by William of Saliceto (1210–1277)⁴ at Bologna, by Lanfranchi (1296) the founder of French surgery,² and by his distinguished pupil, Guy de Chauliac (1300–1368),² the most celebrated authority on surgery in the 14th century; however, the actual practice of such a procedure was rarely undertaken.

Unlike his predecessors whose records contain only passing references to nerve injuries and their treatment, Leonard of Bertapaglia (1380–1463)⁵ devoted an entire chapter in his *Chirurgica* to this subject. However, nowhere in his writing did he provide any reference to the operative details of surgical technique. This was undoubtedly due to his firm belief that these techniques could be learned only by serving an apprenticeship under the tutelage of an experienced surgeon and not from the book.⁵

Without sufficient understanding of anatomy, physiology, and the regenerative capacity of the peripheral nervous system, it is not difficult to comprehend the frustration that might have been encountered by the physicians and surgeons in dealing with severed nerves and their subsequent repair. This was probably the most important reason why the repair of nerves was rarely undertaken in medieval times and why the general consensus was against such practices.^{2,4} Despite the efforts of some surgeons to keep alive the concept of nerve suture, notably Ferrara (1608)⁶ and Arneemann (1787),² the traditional opposition to this procedure persisted well into the 19th century.^{2,6}

During the 16th to 18th centuries, more information was required to increase the understanding of nerves: their excitable nature by Frances Glisson (1597–1677)⁴; their microscopic structure by Antoni van Leewenhoek (1632–1723)⁴; and descriptions of the axon and myelin sheath by Fontana (1730–1805).⁴ The functional aspect of nerve fibers was elucidated by Galvani (1737–1798) in his experiments utilizing frogs and showing their responses to electrical stimulation. Anatomic organization of motor nerve associated with the ventral roots was first recognized by Sir Charles Bell (1774–1842), and the localization of sensory function in the dorsal roots was determined by Francois Magendie (1783–1855).^{7–9} Later, Theodore Schwann (1810–1887) published findings regarding the structure of the cell that bears his name.¹⁰

In the early 19th century, after Johannes von Purkinje (1787–1869) elucidated the connection between neurons and axons, and his contemporary Robert Remak (1815–1855) showed the differentiation of myelinated and unmyelinated nerve fibers,⁹ a milestone in the understanding of nerve injury was reached by Augustus Waller in 1850, who described

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the phenomenon of "Wallerian" degeneration and the loss of the distal nerve element.¹¹ These developments dramatically turned attention to the study of nerve repair.

With a further accumulation of knowledge and an increased understanding of nerve anatomy, function, and physiology, a more precise understanding of the process(es) of nerve healing ensued that initiated the establishment of rational strategies of nerve repair—from wild speculation to a more predictable reality. Studies conducted over the past century have yielded principles guiding today's peripheral nerve repair. Hueter, in 1873, described the traditional method of epineurial repair (Fig. 1) of a transected peripheral nerve,¹² and later in 1917, Langley and Hashimoto advocated the more refined perineurial repair.¹³ This method, was impractical, since the technical refinements allowing its skillful performance were not yet available.⁴

Early peripheral-nerve repair was often represented by a rather crude attempt at restoration of nerve-trunk continuity, without much regard to correct topographic alignment or consideration of tension at the repair. Sir Sydney Sunderland, in his study of the intraneural topography of the radial, median, and ulnar nerves in 1945,¹⁴ and of the sciatic nerve in 1948,¹⁵ provided the anatomic foundation for peripheral-nerve repair. In 1964, Kurze¹⁶ and Smith¹⁷ independently advocated the use of the operating microscope. During the 1970's, Terzis defined the advantages of tension-free repair.¹⁸ These ad-

vancements, along with the use of microsurgical atraumatic techniques, permitted more technically precise methods and allowed for reasonably good fascicular alignment and improved functional outcome (Fig. 2).

Although nerve repair is possible, there are several factors that preclude the possibility of an ideal nerve repair with normal functional restoration: the accuracy of nerve apposition at the repair site; the limited number of donor grafts available for bridging extensive nerve gaps; the number of neurons that remain viable following a severe injury; the condition of their respective target tissue; and the ability to guide and enhance nerve regeneration. The technological progress of nerve repair is still in its infancy. At any time, a landmark development in the foundation of knowledge may forever alter the approach to nerve repair.

Presently, anatomic axon-to-axon reconnection and normal restoration of function after significant nerve injury remain unobtainable ideals; however, ongoing research is making strides toward these goals. Current research includes detailed descriptions of intraneural organization,¹⁹⁻²¹ and clinical application of histochemical²²⁻²⁶ and electrophysiologic²⁷⁻³¹ techniques for sensory motor differentiation (Figs. 3, 4). All of these techniques attempt to reduce the loss of regenerating axons that occurs at the site of the repair, and to maximize the restoration of functionally useful connections with the periphery.

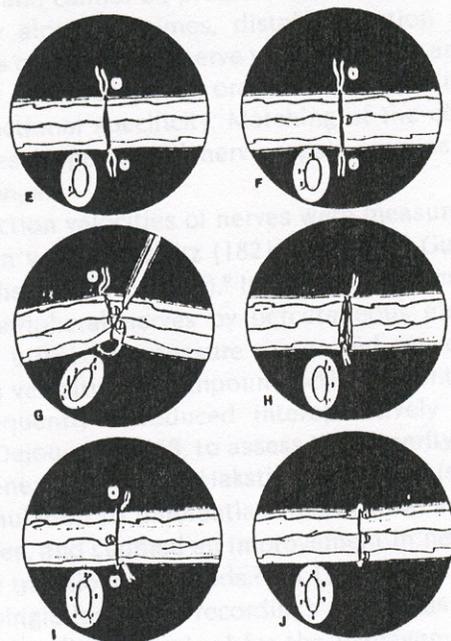
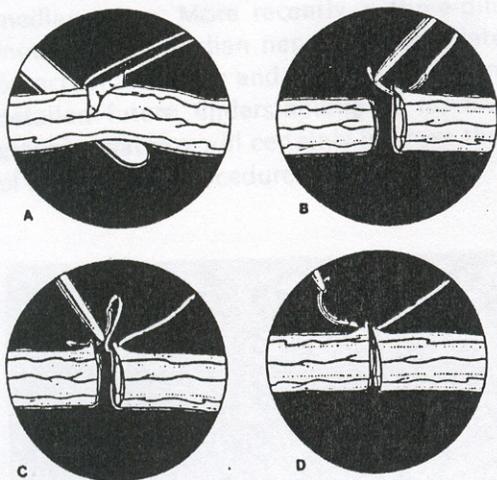
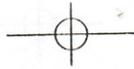


Figure 1. Epineurial repair of nerve. A, Nerve is transected. B, Entry bite of guide suture. C, Exit bite. D, Needle recovery. E, First and second guide sutures have been placed. F, Anterior repair completed. G, The nerve is rotated by pulling upward on the tails of second guide suture to expose the posterior surface. H, Exposure of the posterior surface of the repair is completed. I, Three stitches complete the posterior repair. J, Epineurial repair completed.



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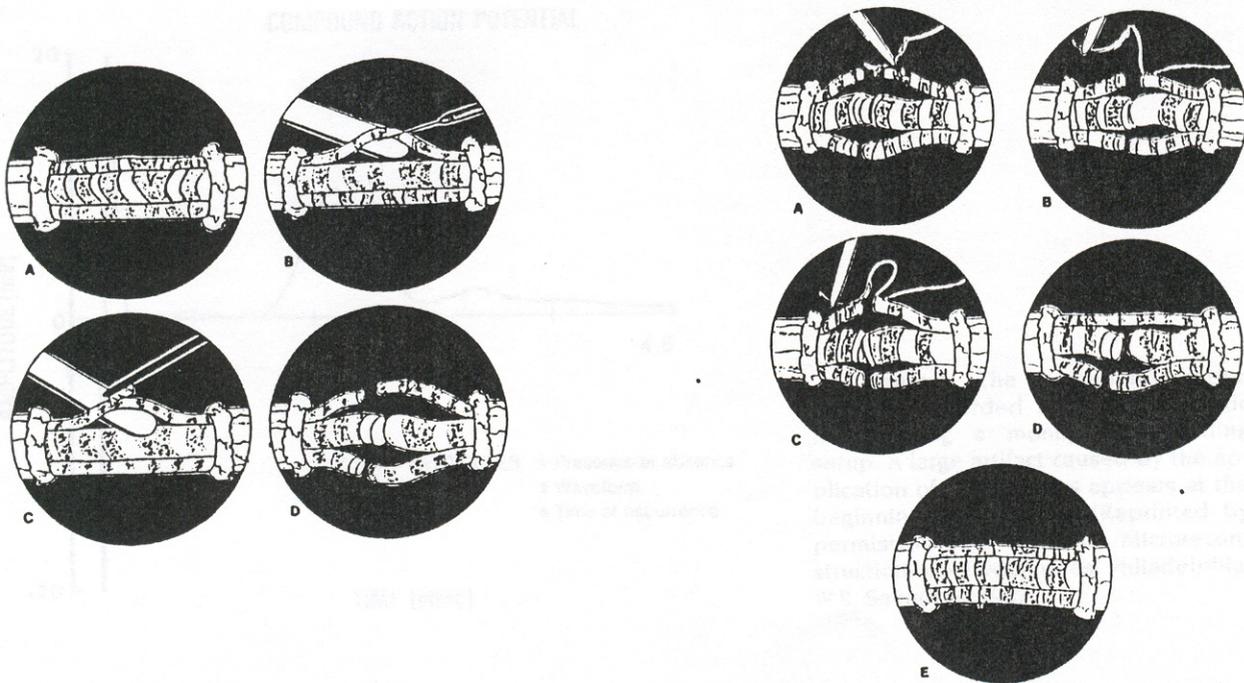


Figure 2. Perineurial repair of a nerve. A, Completion of epineuriectomy. B, Fascicular dissection is achieved with a microneedle. C, Once dissected, each fascicle is sharply transected. D, All three fascicles are transected at different levels to prevent superimposition of the suture lines. E, Entry bite. F, Needle recovery. G, Exit bite. H, Only one suture is required for the repair of the smaller fascicles. I, Perineurial repair completed. (Reprinted by permission from Daniel RK, Terzis JK: *Reconstructive Microsurgery*, Boston: Little, Brown, 1977)

Since the landmark anatomic work by Sunderland,³² many investigations have been carried out further to detail and quantitatively to delineate the intraneural microanatomy of various nerves.¹⁹ For these studies, the question of intraspecies variation remains a concern. Utilizing the advancement of computerized technology, Terzis³³ first looked at the constantly changing intraneural topography of the median nerve. More recently, a three-dimensional model of the median nerve was formulated, based on actual anatomic and histologic sections.²¹ More detailed future understanding of fascicular topographic anatomy will certainly improve the accuracy of nerve-repair procedures.

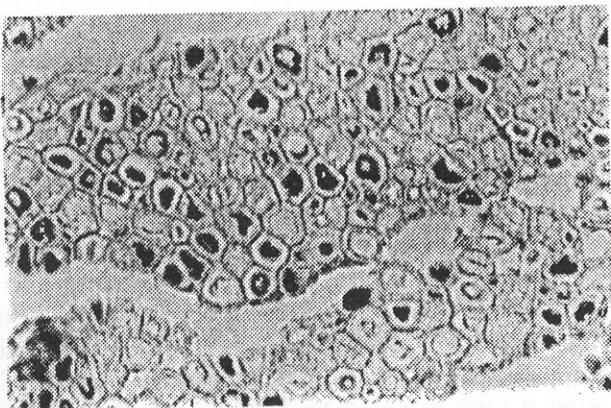


Figure 3. Photomicrograph of section of rat sciatic

As the method of repair becomes more sophisticated, it has become clear that morphologic information alone is not sufficient consistently to identify previously contiguous fascicles for coaptation. Accurate sensorimotor differentiation of the constituent fascicles of an injured mixed peripheral nerve is essential and cannot be predicted on the basis of morphology alone. At times, distal dissection of components of the injured nerve to its branches and targets may be necessary, in order to clearly delineate its functional specificity. Matching of the correct fascicles in peripheral nerve repair remains a great challenge.

Conduction velocities of nerves were measured by Hermann von Helmholtz (1821–1894) and Guillaume Duchenne (1806–1875).⁹ In the 1940's, stimulation of peripheral nerves by percutaneous electrodes was utilized to measure motor and sensory conduction velocities.³⁴ Compound action potential was subsequently introduced interoperatively by Kline and Dejour in 1968, to assess the integrity of peripheral-nerve lesions.²⁸ Hakstian, in 1968, used electrostimulation to differentiate motor from sensory bundles, and claimed an improvement in nerve repair over traditional methods.²⁹ In 1976, Terzis introduced single fascicular recordings (Fig. 5) as an intraoperative diagnostic tool for the management of peripheral nerve lesions in continuity.³⁰ Thus, for the first time, it became possible to access the functional carry-through of individual bundles and to pre-

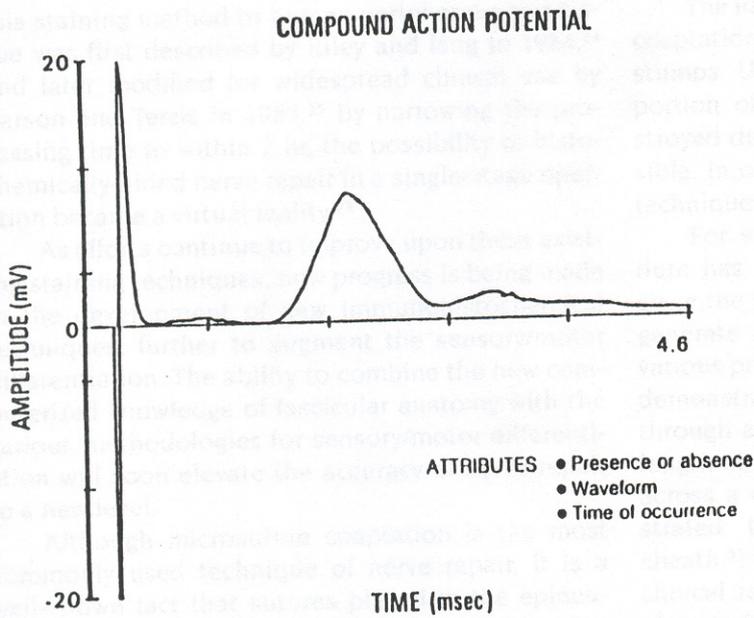


Figure 4. The compound action potential recorded from a frog sciatic nerve using a monopolar recording setup. A large artifact caused by the application of the stimulus appears at the beginning of the trace. (Reprinted by permission from Terzis JK: *Microreconstruction of Nerve Injuries*. Philadelphia: W.B. Saunders, 1987)

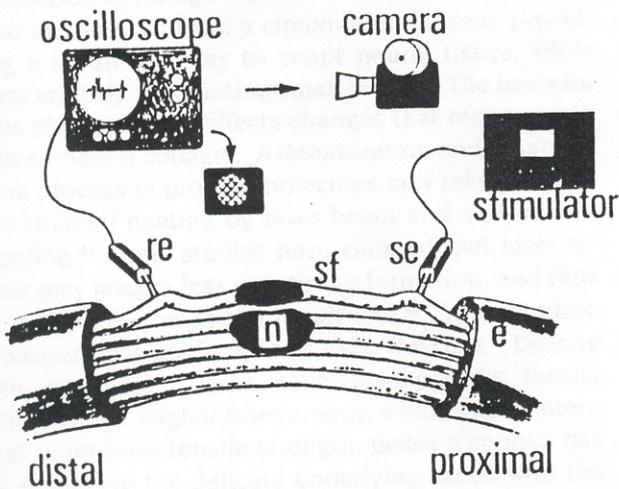


Figure 5. Single fascicular recording setup, where re = recording electrode; se = stimulating electrode; sf = single fascicle. (Reprinted by permission from Terzis JK: *Microreconstruction of Nerve Injuries*. Philadelphia: W.B. Saunders, 1987)

nerve lesion into a complete one. Further understanding and research expanded the use of electrophysiologic recordings in peripheral-nerve surgery and facilitated widespread use.³⁵

Electrophysiologically-aided motor- and sensory-fascicle differentiation has since been an important tool that effects nerve repair,³⁵ and the ability to depict the intraneural composition of sensory and motor fibers within peripheral nerves was realized.³¹

On a separate front, several histochemical methods have been developed to permit differentiation of motor and sensory fibers. A "direct coloring" thiocholine staining for cholinesterase was first described by Karnovsky and Roots in 1964.³⁶ With this histochemical method for acetylcholinesterase

ber *et al.* demonstrated the possibility of sensorimotor differentiation in 1973,³⁷ and subsequently applied it to nerve-reunion operative procedures in 1976.³⁸ Initially, a two-stage procedure was necessary because of the long incubation time required for the staining technique. With continuous improvement, a more rapid ACHE histochemical method is now available with results within 2 hr.^{22,23}

Carbonic anhydrase (CA), an enzyme responsible for the hydration of carbon dioxide, plays an essential role in secretory processes and ion transport in many organ systems. A formal histochemical demonstration of carbonic anhydrase activity was offered by Hansson in 1967.³⁹ Contrary to ACHE staining technique, carbonic anhydrase is selective



this staining method to human peripheral-nerve tissue was first described by Riley and Lang in 1984,²⁴ and later modified for widespread clinical use by Carson and Terzis in 1985.²⁵ By narrowing the processing time to within 2 hr, the possibility of histochemically-aided nerve repair in a single-stage operation became a virtual reality.²⁵

As efforts continue to improve upon these existing staining techniques, new progress is being made in the development of new immunohistochemical techniques, further to augment the sensory/motor differentiation. The ability to combine the new computerized knowledge of fascicular anatomy with the various methodologies for sensory/motor differentiation will soon elevate the accuracy of nerve repair to a new level.

Although microsuture coaptation is the most commonly used technique of nerve repair, it is a well-known fact that sutures placed in the epineurium or perineurium invite fibroblastic proliferation and can cause compression, scarring, and misdirection of axonal tissue.⁴⁰ Laser nerve welding is one of the alternatives attempted, because it avoids the introduction of foreign material into the repair site.⁴¹⁻⁴⁴ The welding can form a circumferential seal, providing a sutureless way to coapt neural tissue, while concurrently coagulating small vessels. The basis for this phenomenon reflects changes that may occur in the epineurial collagen. A denaturation and renaturation process in protein molecules may take place after thermal heating by laser beam and subsequent cooling.⁴¹ Some studies have claimed that laser repair may lead to less scar tissue formation, and thus less constriction at the repair site.⁴² Other studies, however, have not found this to be the case.⁴³ Despite the advantages, laser neurorrhaphy lacks tensile strength.^{42,43} Higher laser energy, which has a potential to improve tensile strength, poses a serious risk of damaging the delicate underlying axons with the thermal effect.⁴⁵ More recent experiments have shown that wrapping various tissues at the repair site not only increases tensile strength, but also protects the coaptation.⁴⁶ With continuing progress, laser neurorrhaphy may play a role in the future of nerve repair.

Since the description of nerve repair using agglutination by Paul of Aegina as early as the 7th century,⁴⁷ and egg albumin by Roger of Parma in the 13th century,⁴⁸ different tissue adhesives have been utilized in nerve repair with varying degrees of success.^{49,50} A more recent experimental endeavor used freezing to trim the nerve, and fibrin glue to coat it before thawing. This procedure demonstrated much better axonal alignment than that obtained by microsuture alone. This manipulation, facilitated by freezing the nerve stump, also reduced axonal disorganization. In addition, fibrin glue was found to allow molecular diffusion and may be used to enhance

The ideal scenario for nerve repair is end-to-end coaptation of the proximal and distal severed nerve stumps. Unfortunately, more often than not, some portion of the nerve has been attenuated or destroyed during injury, making a direct repair impossible. In order to achieve tension-free repair, use of techniques to bridge the existing gap is indicated.

For short defects, the free "tube-graft" procedure has been attempted. It has been recognized since the late 1800's, that a peripheral nerve will regenerate across small gaps, when guided through various preformed conduits.⁵¹⁻⁵³ Recent reports have demonstrated that the maximum regeneration through a nerve conduit in the rabbit model was a length of 3 cm.⁵⁴ In the primate model, regeneration across a distance of up to 3 cm has been demonstrated through a vascularized pseudosynovial sheath.⁵⁵ Chiu and Strauch have demonstrated good clinical regeneration in non-critical sensory nerves of up to 3 cm. in length.⁵⁶ Another clinical study using polyglycolic acid tube reconstruction in digital nerve injuries has met with some success.⁵⁷ Current research indicates that nerve regeneration through a conduit is enhanced when a short segment of autologous nerve is placed within the conduit.⁵⁸ This nerve segment appears to be a source of Schwann cells and trophic factors. Direct utilization of Schwann cells in this regenerative environment has also been documented with favorable effects—even with exogenously cultured Schwann cells.⁵⁹ With the realization that exposure of the regenerating fibers to neurotrophins may result in more functionally appropriate reinnervation of target tissues, the use of appropriately prepared nerve conduits may have a role in the future for primary nerve repair.

For longer nerve defects, utilization of nerve grafts is a better alternative. The first nerve grafts were performed by Phillipeaux and Vulpian⁶⁰ in 1870 and Albert⁶¹ in 1885. Advanced by improved techniques, nurtured by past failures, and equipped with better understanding of the repair environment, the concept of "cable grafting" was introduced by Bunnell and Boyes in 1939.⁶² This was the first attempt to bridge a nerve defect with multiple strands of a sensory nerve graft fashioned to form a cable, rather than a trunk graft with its associated central necrosis. In 1947, St. Clair Strange introduced the first vascularized nerve pedicle for reconstruction of large nerve gaps.⁶³ This set the stage for advances in vascularized nerve grafting. With the advent of microsurgical techniques, transferring of a nerve graft regardless of its diameter and proceeding with immediate revascularization (Fig. 6) became realities.⁶⁴ The concept of improving the blood supply at a nerve-injury site and thus guaranteeing rapid revascularization of the interposition nerve grafts and the coaptation sites, has been one of the greatest ad-

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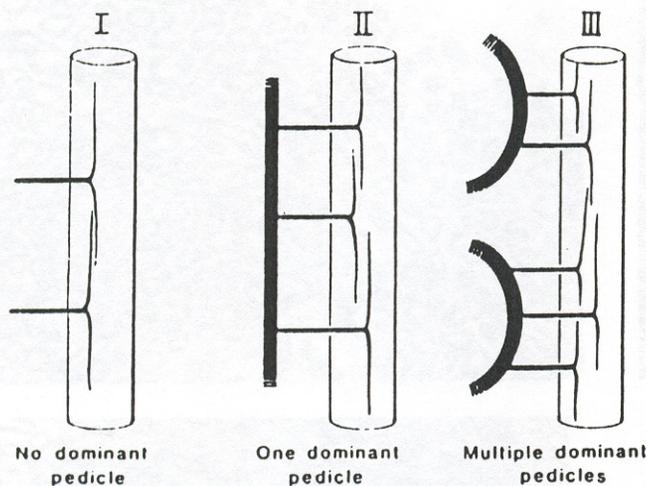


Figure 6. Classification of blood supply to nerves. (Reprinted by permission from Terzis, JK: *Microreconstruction of Nerve Injuries*. Philadelphia: W.B. Saunders, 1987

altered the prognosis of patients with devastating nerve lesions.⁶⁵

Although nerve-graft techniques have become the standard for bridging nerve defects for repair, nerve autografting inevitably involves sacrificing one or more nerves. This disadvantage alone justifies the continued search for a more acceptable substitute. Since the first human nerve allograft was performed in 1878,⁶⁶ experimental and clinical work has been reported periodically. In order for allografts to replace autografts, they must provide results that are consistently superior to, or at least as good as, those of the autograft. This has yet to be convincingly demonstrated.

New developments in the field of immunology have stimulated considerable work in the response of nerve allograft. The results have been variable, and failures were related mainly to rejection, incomplete neural regeneration, and toxicity with the available immunosuppressants, especially with long-term immunosuppression.⁶⁷ The approach to this problem has involved either manipulation of the host's immune system or modification of the donor graft (pretreatment).⁶⁸ Experimental studies have demonstrated that lyophilization and high-dose irradiation were successful in decreasing antigenicity of the nerve allograft⁶⁹; however, the degree of regeneration that occurred across these grafts was significantly inferior than when fresh autografts were used.⁷⁰ New modalities of allograft pretreatment are being tested, and there is the suggestion that preservation improves functional recovery and reduces the requirement for systemic immunosuppressive therapy.⁷¹

Studies directed toward manipulation of the host's immune system as a method of dealing with the nerve-allograft response have been few. Experimental work has shown that continuous cyclosporin

nerve allografts.⁷² Rejection can also be avoided by inducing in the host a tolerant state specific for that graft.⁷³ Allografts so protected appear to function in a way very similar to nerve autografts, as long as the immunosuppressed or tolerant state is maintained. However, because the tissue surrounding the host axons remains allogenic, cessation of the privileged status allows the axons to express their antigenicity, and rejection ensues.^{74,75} A new generation immunosuppressant, FK-506, promises a one-hundred-fold increase in potency and less toxicity, in comparison to cyclosporin A. More important, data indicate that host axon regeneration across peripheral-nerve allografts continues after cessation of immunosuppression with FK-506.⁶⁷ It appears that if continuous research in this field can provide better immunosuppressants with less toxicity for the host, the use of allografts may become a viable alternative over autografts.

Until now, one of the major contributions to the foundation of knowledge was characterization of axon reaction to nerve-trunk transection, originally proposed by Augustus Waller in 1850. Recent advances in the understanding of nerve regeneration (Fig. 7) provide encouragement for new optimism in the surgical treatment of nerve injury. The efforts of neuroscientists and the study of the cell biology of neural regeneration with growth factors have had no real effect on the clinical management of nerve injury until recently.

In addition to the clinical aspects of nerve injury, certain biological aspects of nerve injury and repair must be considered. Two particular biological aspects important for the clinician are the concepts of neurotropism and neurotrophism. Neurotropism implies an ability to influence the direction of nerve regeneration, while neurotrophism refers to an ability to influence the development and maturation of the nerve.⁶

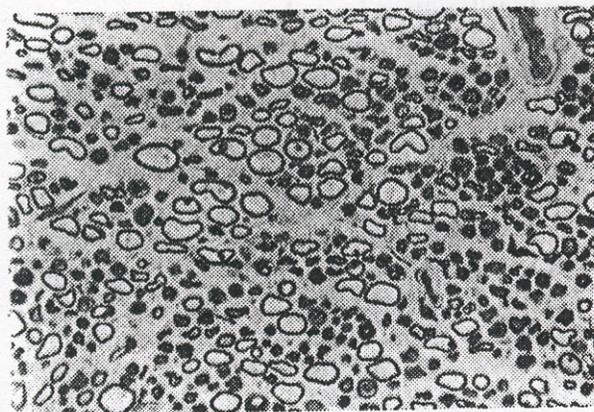
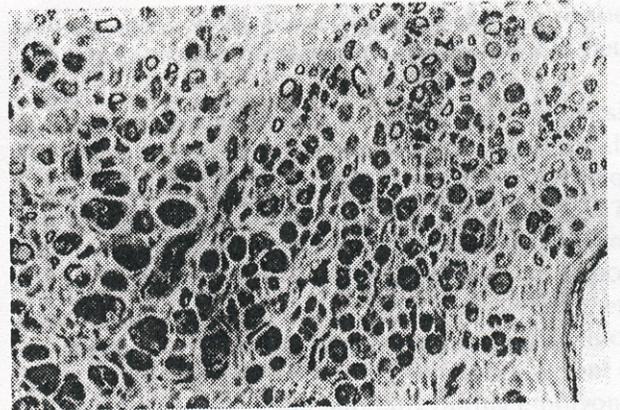
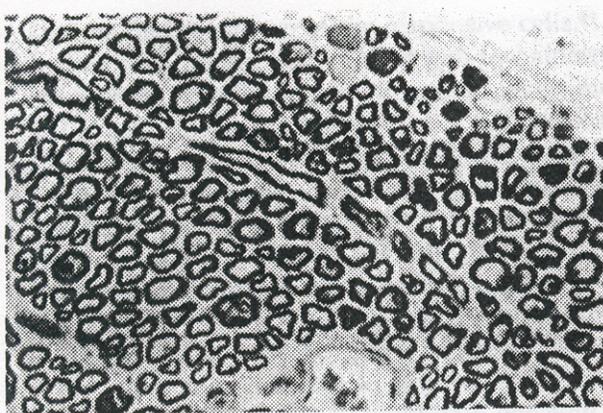
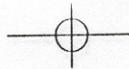


Figure 7. Photomicrograph of rat saphenous nerve stained with toluidine blue. A, normal, B, dener- vated, C, reinnervated (X400).

Forsman⁷⁶ in 1898, concerning the nerve's attraction to its distal stump or its appropriate end organ. In a series of multiple-choice experiments using Y-chambers, Politis⁷⁷ in 1982 demonstrated that regenerating nerve fibers selectively grew down the channel which contained the distal nerve stump, following the concentration gradient of trophic factors. Furthermore, Brushart⁷⁸ demonstrated that regenerating motor nerves favor motor-over-sensory distal stumps.

The neurotrophism concept was first demonstrated by Rita Levi-Montalcini and Victor Hamburger.⁷⁹ They recognized that certain tissues (e.g., mouse salivary gland) could stimulate nerve growth and proliferation in culture. They named this substance "Nerve Growth Factor" (NGF) and with Cohen⁸⁰ in 1959, subsequently identified, isolated, and purified it. This discovery launched a giant surge in research on nerve growth factors. Today, the list of nerve-growth-promoting compounds continues to grow, along with information on their receptor types, concentration, and localization in the CNS and PNS.

A classification of the major neurotrophins based on their receptors is depicted in Table 1.

The strong growth-promoting action of neurotrophic factors has suggested their use in preventing or lessening the dysfunction and death of neurons in nerve injury or disease. Neurotrophic factors today are defined on the basis of their receptors and classified into three major groups: 1) the neurotrophins, which include NGF, Brain-derived Neurotrophic Factor (BDNF), Neurotrophin-3 (NT 3), and Neurotrophin 4/5 (NT 4/5); 2) neurotrophic cytokines which include Ciliary Neurotrophic Factor (CNTF) and Interleukin-6 (IL-6); and 3) fibroblast growth factors (e.g., acidic Fibroblast Growth Factor (aFGF) and basic Fibroblast Growth Factor (bFGF)).⁸¹ There is a further group of other neurotrophic factors, such as: Leukemia Inhibiting Factor (LIF), Insulin-like Growth Factors (IGF), Epidermal Growth Factor (EGF), and Glial Derived Neurotrophic Factor (GDNF).⁸²

All nerve-growth factors exert their influence via binding to particular classes of tyrosine kinase re-

Table 1. Classification of Major Neurotrophic Factors

Groups of Neurotrophic Factors	Examples
I. Neurotrophins	NGF, BDNF, NT3, NT4/5
II. Neurotrophic Cytokines	CNTF, IL 1, 3, 6
III. Fibroblast Growth Factors	aFGF, bFGF



ceptors on the surface of the responsive cells.⁸³ For instance, all neurotrophins bind with low affinity to the p75^{NGFR} and with high affinity to a specific member of a glycoprotein tyrosine kinase (e.g., NGF with trkA, BDNF and NT4/5 with trkB, and NT3 with trkC).⁸² Each receptor, once activated by the ligand/receptor binding, is followed by intracellular signalling pathways involving protein phosphorylation and subsequent gene activation.⁸⁴

Since different neuronal populations respond to specific nerve growth factors, injury or disease in a particular neuronal pool would best be treated by the administration of the appropriate nerve-growth factor. A preliminary, but exhaustive, list of neuronal pools and the specific neurotrophic factors that are the best candidates for treating these neurons has been recently reported⁸² (Table 2).

These neurotrophic factors play an important role in the growth, development, and maturation of neurons in both the CNS and PNS. Furthermore, they are therapeutic tools in that they can prevent or reverse the degeneration of neurons caused by mechanical, environmental, or genetic insults. In addition to therapy for nerve injury or disease, neurotrophic factors may be implicated in the pathogenesis, such as an abnormality in the receptor for a specific neurotrophic factor. Another possibility is that the problem lies beyond the receptor, in the signal transduction pathway.⁸²

When examining biological aspects of nerve repair and therapeutic treatment, it is essential that effective specific markers be developed, associated with the various anatomic, biochemical, and genetic changes that are correlated with nerve injury and neuronal death. For example, anatomic markers would identify the morphologic changes that are associated with nerve injury, such as chromatolysis and increased lysosomal activity.

In addition, biochemical markers would be more specific and clearly associated with neurotransmitters, enzymes, proteins, and ion levels. Mattson⁸³ reported that intracellular calcium homeostasis via various influx and efflux mechanisms was critical for neuronal viability, and that nerve injury or excitotoxic insult resulted in an increased intracellular Ca⁺² influx and subsequent nerve degradation, caus-

ing neuronal death. Similarly, the activation of specific proteins (e.g., protein kinases) resulted in neuronal death.

Neuronal death can be divided into apoptosis (a programmed, developmental type of cell death) and necrosis (a cell death due to a non-programmed event such as the result of trauma). For the past 75 years, apoptosis has been known to be a form of cell death distinct from necrosis, as well as an important regressive event during the normal development of the nervous system. For instance, in the chick, mouse, rat, and human, approximately 50 percent of postmitotic neurons die naturally during embryonic or fetal development. It is generally accepted that neurons die during this period of apoptosis. After the period of naturally-occurring cell death, the surviving neurons may later undergo degeneration due to injury or disease.

Recently, apoptosis has been suspected of involvement in the abnormal neuronal death that occurs in neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) and Alzheimer's.⁸⁵ This cell death might be prevented by different agents, including neurotrophic factors.

Finally, there are genetic markers that are utilized in the development of a gene therapeutic model for peripheral-nerve regeneration. It has been demonstrated that there is an upregulation in expression of certain genes in response to nerve injury.^{82,86,87} These genes are called "immediate-early genes" (IEGs) and are activated upon nerve injury by a yet unknown mechanism. However, administration of growth factors after nerve injury does prevent the expression of these IEGs.⁸² Sheng and Greenberg⁸⁷ reported that the mechanism of activating IEG expression involved an increase in intracellular Ca⁺² and CAMP. Examples of some of these IEGs are c-fos, c-jun, and junB. Other examples of gene expression associated with nerve injury and neuronal death are the SGP-2 gene⁸⁸ and the hsp70 gene.⁸⁹

There are many genetic events that determine neuronal phenotype during nervous-system development. Following maturation, the neuronal phenotype is usually static for the remainder of life, unless an injury or degenerative event occurs. Injured neurons may follow one of three potential scenarios:

Table 2. Neurotrophic Factors and Their Responsive Neuronal Populations.

<i>Responsive Neuronal Populations</i>	<i>Neurotrophic Factors</i>
A. Sensory Neurons	NGF, BDNF, NT-3, NT4/5, CNTF, IGF-I, IGF-II, PDGF, TGF, FGF1, FGF2, LIF, GDNF
B. Autonomic Neurons	NGF, BDNF, NT3, CNTF, LIF, IGF-I, IGF-II, FGF1, FGF2
C. Motor Neurons	BDNF, NT3, NT4/5, GDNF, TGF, IGF-I, IGF-II, FGF1, FGF2, FGF3, CNTF, LIF





death, atrophy, or recovery. The ability of injured, adult neurons to recover from injury may be determined by events that also influence neuronal phenotypes during development, including expression of growth-related genes, and response to survival and growth signals in the environment. The latter signals include neurotrophic factors and substrate molecules that promote neurite growth.

When both neurotrophic factors and growth-promoting substances are provided to the adult nervous system following axotomy, partial morphologic and behavioral recovery can be induced. Gene-therapy techniques, such as the use of a replication-deficient retrovirus carrying a desired specific gene, are useful tools for providing these substances. Gene therapies locally deliver genes important for nerve regeneration to nerve and muscle without tissue degeneration.^{90,91}

Presently, these techniques are becoming quite popular—for example, the intrastriatal implantation of fibroblasts⁹² or astrocytes⁹³ genetically engineered to produce BDNF and prevent degeneration of dopaminergic neurons in Parkinson's disease. These studies suggest that gene therapy with BDNF can ameliorate parkinsonian symptoms. Similarly, fibroblasts genetically modified to release CNTF have been shown to be a potential delivery system in treating ALS.⁹⁴ With the advancement of genetic engineering, gene therapy will find its proper place in the area of post-traumatic neuroorrhaphy.

Gene manipulation and cloning are also existing technologies. A new discipline of tissue engineering is emerging, in which the principles of engineering and the life sciences are applied for the generation of biologic substitutes, which are aimed at the creation, preservation, or restoration of lost organ function. The problems of nerve-grafting deficiency in the future may be alleviated by the genetic cloning of nerve fibers. With the aid of neurotrophins, it may be soon possible to approach nerve injury *de novo* via genetic engineering, with complete regeneration eliminating the need for repair. Without the inherited problems associated with conventional nerve repair, perfect restoration of function may therefore be achieved.

Yesterday's "Star Wars" can be today's reality. As we move toward a new millennium, we can believe that the amalgamation of modern technology, telecommunication systems, modern engineering, and medicinal breakthroughs will result in an explosion of knowledge that will enhance our understanding of developmental biology and will culminate in a new era in medicine, enabling us to restore lost tissue function. It has become more apparent that improved clinical results are likely to be realized from a greater understanding of the neurobiology of nerve repair. Intimate collaboration between modern tech-

vancement toward this goal. The endpoint is limited only by the extent of our imaginations.

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