SYNTHETIC NERVE GUIDE IMPLANTS IN HUMANS: A COMPREHENSIVE SURVEY

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OBJECTIVE: Lesions of the peripheral nervous system result in the loss of sensory and motor function and may in addition be accompanied by severe neuropathic syndromes originating from aberrant axonal regrowth. The transplantation of autologous nerve grafts represents the current "gold standard" during reconstructive surgery, despite obvious side effects. Depending on the demands of the lesion site, various donor nerves may be used for grafting (e.g., the sural, saphenous), sacrificing native functions in their target areas. Recently, several synthetic nerve guide implants have been introduced and approved for clinical use to replace autologous transplants. This alternative therapy is based on pioneering studies with experimental nerve guides.

METHODS: We present a comprehensive review of all published human studies involving synthetic nerve guides.

RESULTS: Data from some 300 patients suggest that for short nerve defects of a few centimeters, resorbable implants provide promising results, whereas a number of late compression syndromes have been documented for nonresorbable implants.

CONCLUSIONS: To treat longer defects, further implant development is needed, a goal that could be achieved, for example, by more closely imitating the intact nerve architecture and regulatory cell-cell interactions.

KEY WORDS: Human studies, Lesion, Nerve guides, Polymer, Regeneration

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In the United States some 360,000 patients experience paralytic syndromes of the upper extremities annually (17). Approximately 100,000 patients undergo neurosurgery of the peripheral nervous system in the United States and Europe each year. Typical symptoms are sensory and motor defects that could result in complete paralysis of an affected extremity or development of intractable neuropathic pain. Pain symptoms can also result from aberrant axonal regrowth and neuroma formation after a nerve has been injured. Nerve lesions are caused primarily by accidents, tumors, infections, or the iatrogenic side effects of various surgeries, such as orthopedic interventions or from tooth extraction or aesthetic facial surgery, which could result in facial paralysis (6, 20).

A common characteristic of neurotmesis is the complete interruption of peripheral nerves, which implies transection of neuronal cell processes, whereas in most cases, the corresponding neuronal cell bodies located a fair distance away (e.g., in the spinal cord) remain unaffected. The intact neuronal somata provide the basis for the long-lasting regenerative capacity in the largely permissive microenvironment of the peripheral nervous system. In the context of this review, only injuries of the neurotmesis type (45) will be considered because only this form of trauma has been treated clinically by the implantation of synthetic nerve guides. In less severe cases of neurapraxia and axonotmesis injuries, where either the axonal fibers or the surrounding non-neuronal tissue of the epineurium remain intact, the likelihood of spontaneous regeneration forbids implantation of nerve guides. On the other hand, a missing nerve segment of only a few millimeters abrogates adequate regeneration. For these cases, nerve-grafting procedures are obligatory to overcome the anatomic defect. Typically, implants must merely bridge an existing gap between proximal and distal nerve stumps. Implants do not need to reconnect the proximal nerve stump

with the synaptic target organ because once axons have been channeled into the distal nerve segment by a nerve guide implant, they are directed within the endoneurial tube, which represents the ultimate guiding cue. Consequently, the length of implants is similar to the extent of the lesion itself and not much longer.

Various synthetic nerve guide implants have been tested to replace autologous nerve transplants. In animal experimentation focused on nerve tubulization, a broad range of materials (e.g., extracellular matrix components and synthetic polymers) as well as various designs (multichannel, longitudinal filaments, electrets with stimulatory elements) and additives such as recombinant proteins or growth factor-producing coimplanted cells have been used (23, 41, 43). Pioneering work in humans was performed by using simple silicone tubes (24).

AUTOLOGOUS NERVE TRANSPLANTATION

The autologous nerve grafting procedure still represents the "gold standard" in surgical treatment of defects in the peripheral nervous system. It was Millesi (36) who first demonstrated the value of autologous nerve grafting in his animal studies. In addition, he verified that an autologous graft placed into a defect without tension always resulted in better patient outcome than primary nerve sutures performed under tension (37). As a result, autologous nerve grafts became increasingly favored compared with secondary nerve sutures.

With the increasing popularity of autologous nerve grafts, the discussion arose about the ideal nerve for the grafting procedure (5). Today, the nerve most commonly used for autologous grafting is the sural nerve, which is easy to harvest from behind the outer ankle of the leg, leaving only minor sensory deficits (16). Alternatively, the medial cutaneous nerve of the forearm may be used for autologous grafting. This nerve is suggested for use in cases of brachial plexus injuries (49). After exposition of the infraclavicular portion of the brachial plexus at the axilla, this nerve graft is reported to be easily accessible.

Recently, Matsuyama et al. (32) demonstrated in their studies the importance of the right choice of grafting nerve. They described better results with smaller nerve grafts, hypothesizing that central graft necrosis may occur in cases where grafts with larger cross sections are used. This central necrosis may arise from a state of hypoperfusion of the inner central areas of the grafts, indicating the necessity of a sufficient vascular supply. Therefore, the area surrounding the graft should be of a certain vascularity to ensure adequate graft nutrition. Thus, vascular pedicled grafts were developed and are sometimes used clinically, depending on the anatomic location of the site of injury (9).

Nevertheless, all of the described types of nerve grafts have one disadvantage in common: they all require a second surgical step to harvest the nerve. Donor side morbidity and painful neuroma formation may occur as an unwanted side effect of nerve elevation. Other restrictions are the limited availability of autologous transplant material (sural nerve, approximately 25–30 cm) and the potentially inappropriate diameter of approximately 1.5 mm of most selected nerves. Finally, although various studies have been published that report complete restoration of function or sensation after autologous nerve grafting, the results are normally far from being satisfactory (42).

HUMAN STUDIES USING SYNTHETIC NERVE GUIDES

Published human studies of synthetic nerve guides have thus far been limited to four different materials (1, 10, 34). Two of these materials are nonresorbable inert polymers, silicone and expanded polytetrafluoroethylene (PTFE), and two are resorbable synthetic polymers, polyglycolic acid polymer (PGA) and polylactide-caprolacton polymer (PLCL). In this survey, we summarize for the first time all of the 23 reports published to date, which together comprise data from approximately 300 patients (*Table 1*).

Silicone Nerve Guides

The material aspects of silicone polymers are high molecular weight compounds made of silicon, oxygen, and hydrogen. Depending on the selection of organic side-chains and the ratio of side-chain lengths to crosslinks, numerous characteristics including elasticity can be imparted. Silicone polymers are hydrophobic and are considered physiologically well accepted (*Table 2*).

In the first case studies, six patients with nerve lesions in the upper extremities were documented (24, 25, 35). The defects of the ulnar and median nerve comprised a few millimeters and had caused sensory defects; in addition, paralysis of the hand was evident in some cases. Short silicone tubes were implanted and resulted in oriented axonal regrowth as deduced from recovery of sensory and motor function in the hand. However, intolerance to cold temperature and hypersensitivity accompanied the regeneration in several instances. Consequently, some implants were removed from patients after 2 to 3 years without disrupting the initial recovery (7). The most likely cause of these complications was compression of axons inside the nonresorbable nerve guide because the cross-sectional area of nerve fibers increases with the degree of myelination. This would also explain why only late-onset adverse effects have been reported after the initial period of progressing regeneration. In addition, insufficient matrix formation has been discussed as inhibitory cause (8).

The randomized, clinical, prospective study that compared 18 patients with hand injuries (age, 12–72 yr) included direct coaptation of nerve ends (seven patients) and tubulation with silicone tubes (11 patients) (26). Because of the comparison with coaptation, the defect distance could not be longer than 4 mm. Responses to implantation were assessed with various sensory and motor function tests (tactile two-point discrimination, perception level for vibrations of multiple frequencies, pressure detection). One year after surgery, substantial recov-

TABLE 1. Human implant studies and case reports[a]

Series (ref. no.)	No. of patients	Age (yr)	Nerve	Material	Defect length (mm)	Follow-up (mo)	Outcome
Merle et al., 1989 (35)	3	26–37	Median nerve	Silicone	3	11	–
Lundborg et al., 1991 (24)	1	21	Ulnar nerve	Silicone	3	36	+
Lundborg et al., 1994 (25)	2	12, 21	Median nerve	Silicone	3–5	36	–
Lundborg et al., 1997 (26)[b]	11+7 ctrl	12–72	Median/ulnar nerves	Silicone	3–5	3-11	+/-
Luo et al., 1997 (28)	11	?	Median/ulnar/radial nerves	Silicone	30–50	12–60	+
Braga-Silva, 1999 (3)	26	18–26	Median/ulnar nerves	Silicone	20–50	14–40	–
Dahlin[b] (7)	7	15–49	Median/ulnar nerves	Silicone	3–5	12–44	–
Lundborg et al., 2004 (27)[b]	17 + 13 ctrl	12–72	Median/ulnar nerves	Silicone	3–5	3–60	+
Stanec and Stanec (48)	1	22	Ulnar nerve	PTFE	29	36	+
Stanec and Stanec (47)	43	9–56	Median/ulnar nerves	PTFE	15–60	24–37	+/-
Pogrel et al., 1998 (40)	5	16–56	Inferior alveolar/lingual nerves	PTFE	2–15	36	–
Pitta et al., 2001 (39)	6	21–49	Inferior alveolar/lingual nerves	PTFE	3	12–36	–
Mackinnon and Dellon, 1990 (30)	15	Ø 30	Digital nerves	PGA	5-30	11–32	+
Crawley and Dellon, 1992 (6)	1	51	Inferior alveolar nerve	PGA	25	24	+
Weber et al., 2000 (50)	98[d], 62 PGA +74 ctrl	17–65	Digital nerve	PGA	2–12	3–12	+
Kim and Dellon, 2001 (18)	1	11	Medial plantar nerve	PGA	20	10	+
Hagiwara et al., 2002 (13)	1	?	Rectum	PGA	?	4	+
Inada et al., 2004 (15)	2	56, 62	Digital/superficial peroneal nerve	PGA	20–65	6	+
Inada et al., 2005 (14)	2	30, 49	Digital nerve	PGA	25–36	9–12	+
Navissano et al., 2005 (38)	7	Ø 26	Facial nerve	PGA	10–30	7–12	+
Battiston et al., 2005 (1)	17 + 13 ctrl	15–67	Digital nerve	PGA	10–40	6–74	+
Meek et al., 2003 (33)[c]	2	28, 50	Digital nerve	PLCL	5–12		+
Bertleff et al., 2005 (2)[c]	17 + 13 ctrl	Ø 43–38	Digital nerve	PLCL	2–20	3–12	+

[a] All peer-reviewed publications on synthetic nerve guide implants in humans are summarized (April 2006). Numbers of patients represent those people who received synthetic nerve guide implants. Patient numbers of control groups (nerve coaptation or autologous transplants) are marked ctrl. Age, range of age, or mean age (Ø) indicated depending on data provided by corresponding publication. Unknown data denoted with a question mark (?). Implant materials were silicone, polytetrafluoroethylene (PTFE), polyglycolic acid (PGA), and polylactide/caprolacton (PLCL). Outcome of studies were qualified as positive (+) if 75% of patients displayed good or very good results or were not significantly different from control group. Outcome was classified as negative (–) if success rate was less than 75%. +/–, regeneration was initially positive but partially failed after longer period, which made it necessary to remove some implants or that one subgroup of patients displayed poor recovery.

[b, c] Publications with same letter represent data from same cohort at different time points.

[d] Publication presents 98 patients with 136 nerve lesions; it was not stated how many patients received indicated 62 PGA implants.

TABLE 2. Approved nerve guide implants[a]

Product name	Material	Diameter × length	Degradation time	Company
Neurotube	Polyglycolic acid	2-8 mm × 4 cm	3 months	Synovis Micro Companies Alliance, Birmingham, AL
NeuroMatrixNeuroflex	Type 1 collagen	2-6 mm × 2.5 cm	7 months	Collagen Matrix Inc., Franklin Lakes, NJ
Neurolac	Poly-DL-lactide-*-caprolactone	1,5-10 mm ××x 3 cm	16 months	Polyganics BV, The Netherlands
NeuraGen	Type 1 collagen	2-7 mm × 2 cm	4 years	Integra Neuroscience, Plainsboro, NJ
SaluBridge	Polyvinyl alcohol hydrogel	2-10 mm ××x 6.35 cm	No degradation	SaluMedica LLC, Atlanta, GA

[a] Nerve guide implants approved by the U.S. Food and Drug Administration for human application listed. Implants are produced from nonresorbable polymer (1x) and resorbable materials (4x) with different degradation profiles. To our knowledge, peer-reviewed human data have been published only for Neurolac and Neurotube.

ery was reported, with essentially no difference between techniques. However, 1 to 3 years later, some patients complained of local discomfort. Implants were removed in seven cases, leaving the regenerated nerve unaffected (7, 26). The same initial groups of patients were assessed 5 years after implantation (27). Most notably, progressive improvement of functional sensitivity was evident throughout the 5 years, with no statistical difference between groups except that cold intolerance was significantly less severe in the tubular technique group.

In one study, 26 patients aged 18 to 26 years with lesions of the upper extremities received implants up to 5 cm in length. In most cases, regeneration was satisfactory, although silicone implants again needed to be removed in seven subjects (3).

In another study, 11 patients with 15 longer nerve defects (30–50 mm, hand and lower arm) received silicone tube implants (28). Pressure sensitivity and motor function were evaluated during postsurgery periods between 1 and 5 years. Excellent recovery was reported in eight cases, with the other patients displaying good recovery, with the exception of two, who failed to reach an acceptable level of regeneration.

Polytetrafluoroethylene Nerve Guides

In terms of material aspects, PTFE is extremely inert because of the highly electronegative nature of fluorine and the resulting strong binding to carbon atoms. The pronounced surface tension makes PTFE highly anti-adhesive. PTFE is considered physiologically harmless. PTFE can be mechanically expanded, a property that is now widely used to produce microporous membranes (GoreTex).

The first report describes a PTFE tube implantation (GoreTex) into a 22-year-old woman 5 months after she had experienced a transection of the right ulnar nerve leading to paralysis of the hand and loss of sensation (48). During the 5-month period, a neuroma had formed at the site of injury. The neuroma was a benign and localized but very painful tumor that originated from an aberrant regeneration process. After dissection of the neuroma, the 3-cm defect distance was bridged with a hollow PTFE tube 6 mm in diameter. Three years later, excellent motor and sensory recovery was reported, although the patient complained about some irritation in the wrist area during hand motion.

The same authors published a study with 43 patients who experienced nerve lesions ranging from 15 to 60 mm in the lower arm (47). The average delay between trauma and treatment was 4 months. Two to 3 years later, three-quarters of all patients with short defects (15–40 mm) displayed good recovery, as judged from cutaneous touch and/or pressure thresholds, static and moving two-point discrimination, and grip strength. Longer defects (41–60 mm) resulted only in 13.3% of all cases providing useful reinnervation.

Pogrel et al. (40) implanted nonresorbable GoreTex nerve guides into five patients aged 16 to 56 years to bridge lesions of 2 to 15 mm length in different facial nerves. Implantations were performed 4 to 30 months after the initial trauma had occurred. Three years later, postoperative assessment revealed recovery of two patients. Temperature and tactile sensitivity of three subjects remained moderate or poor.

In another study, six cases with GoreTex vein graft tubing as a conduit for the repair of inferior alveolar nerves and lingual nerves were reported (39). Nerve reconstruction with 3-mm diameter tubing was performed an average of 20 months after injury. On the basis of the assessment of pain levels, touch, cold sensation, and two-point discrimination, the clinical outcome was considered poor, although some regeneration was evident in several subjects.

In summary, the majority of data suggest that nerve guides support neuronal regeneration but that nonresorbable implants may cause late adverse effects, especially compression of pressure-sensitive axons. This can be avoided by choosing larger implant diameters for tubulization. However, to date, most surgeons seem to prefer fully resorbable implants, as described below. Most notably, even Lundborg et al. (27), who have been heavily involved in partially successful silicone-based nerve tubulization, reported quite recently, "there is no convincing evidence to encourage the use of silicone tubes."

Polyglycolic Acid Nerve Guides

In terms of material aspects, PGA is resorbable. Hydrolysis, which is initially independent of cells and released enzymes, yields glycolate, pyruvate, and, finally, $H_2O + CO_2$ as the end products. During this process, a transient pH decline is observed. For this reason, the amount of polymer material implanted should be limited; otherwise, the resulting acid cannot be neutralized by the cellular microenvironment and would lead to necrosis. The hydrolytic process can be governed by the preselection of compounds for production and postproduction methods, such as irradiation to partially break covalent linkages within the polymer. Thus, more or less defined degradation periods can be designed. PGA has been widely used as a suture material in the clinical setting.

For the first study with PGA nerve guides, 15 patients with 5- to 30-mm long lesions of hand nerves were enrolled (30). Eleven to 32 months later, a final sensory evaluation using two-point discrimination tests was performed. Thirteen patients had achieved a good or very good level of recovery, and only two patients displayed poor regeneration. In summary, the synthetic implant was qualified as equivalent to autologous nerve transplants.

A 51-year-old patient experienced a trauma of the inferior alveolar nerve after extraction of one molar with subsequent persistent paresthesia of the lower lip and articulation problems. The developing facial pain required continuous pain medication. Sixteen months later, the 25 mm nerve gap was bridged by PGA tubulization. After surgery, complete relief from facial pain was reported, and 2 years later, sensory and motor function had nearly completely recovered (6).

The largest multicenter study in the United States for the first randomized, prospective evaluation of resorbable PGA nerve guides included 98 patients (age, 17–65 yr) with 136

lesions of hand nerves (50). Patients were treated in two groups: either autologous transplants and/or direct coaptations (74 nerves) or PGA tubes (62 nerves) were used. Direct coaptation was used only for short defects. Longer defects were 7.0 ± 5.6 mm (mean ± standard deviation). Three, 6, 9, and 12 months after surgery, a blinded observer measured the two-point discrimination. Sensitivity of the skin was qualified by two tests. In both groups, the recovery of approximately three-fourths of all patients was good or very good, with no statistically significant difference between groups ($P = 0.46$). Nerves repaired by PGA implants resulted in excellent results in 44%, good results in 30%, and poor results in 26%. Nerve repair of the control groups resulted in excellent recovery in 43% of the cases, good results in 43%, and poor results in 14%. Interestingly, regeneration over distances greater than 4 mm was superior in the group with PGA implants. The mean moving point discrimination was 3.7 ± 1.4 mm for PGA and 6.1 ± 3.3 mm for end-to-end repairs. All nerves with deficits of 8 mm or more demonstrated better regeneration with PGA tubes, 6.8 ± 3.8 mm with excellent results obtained in 7 out of 17 nerves, whereas the mean moving two-point discrimination for the graft repair was 12.9 ± 2.4 mm, with excellent results obtained in none of the eight nerves.

Two reports presented two patients with PGA implants. An 11-year-old boy had developed a very painful neuroma 5 years after an injury to his foot. After resection of the neuroma and subsequent axonal regrowth via the PGA implant, the boy had recovered completely and participated in sports (18). Considerable improvement was also observed with a patient who had a tumor and was treated after surgical resection of recurrent intrapelvic rectal cancer. This is one of two publications in which a nerve guide was filled with a collagen matrix (13).

After neuroma resection, collagen-filled PGA nerve guides were also implanted into two elderly patients (aged 56 and 62 yr) to cover nerve defects of 65 and 20 mm in the leg and hand, respectively (15). Functional tests several months later included laser Doppler fluxmetry to monitor micro perfusion, thermography, sensation, and electrophysiological recordings. Overall, excellent recovery of sensory and motor function was documented. The same group presented the most recent report on two women (aged 49 and 30 yr) with "the worst imaginable pain" approximately 1 year after injury of different finger nerves. The resection of expanded neuromas resulted in immediate pain relief in both patients. Implantation of 3- to 4-cm long PGA nerve guide tubes (3 mm in diameter) filled with a collagen sponge resulted in elimination of any discomfort and essentially complete recovery of motility and sensitivity. Two years later, both patients expressed "great satisfaction" with the outcome (14).

Another report presented seven young patients (average age, 26 yr) who received PGA implants approximately 2 weeks after trauma to cure lesions of terminal branches of the facial nerve (38). Up to 1 year postoperatively, no discomfort or intolerance was reported. The recovery of facial muscle control (e.g., m. orbicularis oris) was good or very good in five subjects and fair in two.

Recent publications summarize data from 30 patients who received either biological implants (autologous muscle-vein conduits, 13) or PGA implants (17 patients) (1). All patients had severed digital hand nerves with gaps of 1 to 4 cm. Approximately half of the patients were treated immediately in the emergency room, whereas treatment of the others took place from 1 to 16 months after the initial trauma. Follow-up of recovery was performed between 6 and 74 months postoperatively. According to data obtained in the two-point discrimination test, recovery was comparably good in both groups. In the PGA group, 16 out of 17 patients demonstrated good or excellent functional regeneration.

Polylactide-Caprolacton Nerve Guides

In terms of material aspects, polylactide polymers are biologically resorbable polyesters of lactic acid. Two optically active isomers exist: poly-L-lactic acid is paracrystalline, and thus fairly rigid and brittle compared with poly-D-lactic acid, which is amorphous and flexible. Copolymerization with caprolacton allows for modification of crystallinity pliability and melting points, all of which affect degradation characteristics during hydrolysis. Polylactide degradation occurs in two phases. In the first phase, high molecular weight polymers are broken down into smaller fragments via pure hydrolysis. The second phase involves an enzymatic degradation that results in complete resorption. The primary end product is lactic acid, which is also known to occur during saccharide metabolism in cells. Similar to PGA, PLCL resorption is accompanied by a transient though less pronounced pH decline.

Although a preliminary study only documented the implantation of PLCL nerve guides but not the regeneration outcome (33), a multicenter study by the same authors presented 30 patients with up to 20 mm long lesions of hand nerves (2). Patients were randomized for treatment either with autologous nerve implants or with PCLC nerve guides. During a period of 1 year, patients were monitored every 3 months with regard to touch and pressure sensitivity. Functional recovery was similarly good in both groups.

APPROVED NERVE GUIDES FOR HUMAN APPLICATION

The depicted data support the notion that the regeneration success obtained with resorbable synthetic nerve guides is equivalent to that achieved with autologous nerve grafts, which result in recovery in the range of 0 to 69% (11, 12, 21, 29). Whereas some authors consider the results after nerve grafting (e.g., in the upper extremities) poor, others reported 89% transmittable action potentials across lesions and useful function after neurolysis (19). In general, younger patients and shorter defects resulted in better restoration of neural function. Furthermore, delayed innervation after injury is disadvantageous because the nerve itself (glia and connective tissue compartments) as well as the target organ progressively degenerate and eventually deteriorate irreversibly. In view of

these limitations, it is noteworthy that various studies report functional regeneration in the elderly (more than 60 years of age) and after implantation delays of more than a year after the initial trauma.

Consequently, the industry has started to appreciate not only the medical benefit but also the commercial potential of synthetic nerve guides. To date, human application has been restricted to the peripheral nervous system, although it is obvious that paralytic patients experiencing spinal cord lesion (incidence, 30,000) (31) could benefit from conduit implants to bridge secondary cysts in the spinal cord. In the meantime, five companies in the United States and The Netherlands have started to address this issue. The first approval of a nerve guide was in 1999. All approved products are hollow tubes made either from resorbable PLCL, PGA, collagen, or a non-resorbable polyvinyl alcohol-based hydrogel (*Fig. 1; Table 2*). Inert silicone and PTFE have not been commercialized to our knowledge. It is evident that all approved implants are limited in their length and represent an alternative to autologous nerve implants for short nerve defects. A number of studies indicate that longer defects require advanced implants, which are under investigation but are not yet available.

BASIC NERVE GUIDE PRINCIPLES

Various types of nerve guides as potential implants have been developed and analyzed with in vitro and animal experimentation. In addition to biological guides such as nerve ghosts (nerve segments deprived of living cells), inverted veins, or muscle-filled veins of auto-, allo-, or xenogenic origin, a broad spectrum of synthetic nerve guides have been investigated. Basic nerve guide principles are met in most cases. Common to most approaches is that nerve guides represent guiding hollow tubes in which the lumen provides the space for axonal regeneration. The implant tube must fit (i.e., slightly exceed) the cross-sectional area of the proximal and distal nerve stump diameter. Therefore, nerve conduits should be available in adequate sizes and lengths. The tube should resist compression but be flexible enough to prevent mechanical irritation. It should be of sufficient tensile strength to allow microsurgical adaptation to nerve stumps. The implant material should be highly biocompatible and not cause inflammation, irritation, or scarring. Ideally, the implant material should be completely resorbed after regeneration is complete. To guarantee sufficient diffusion of oxygen and metabolites, the nerve guide wall should be semipermeable. Ideally, the pore sizes of the wall are designed with a minute diameter to prevent infiltration of scar forming fibroblasts.

Although the microanatomy of native nerves can only be imitated to a limited extent by implementing these parameters, the successful human studies of synthetic nerve guides presented in this study clearly prove the concept to be valid. Nevertheless, constraints still exist, making clear the need for further development.

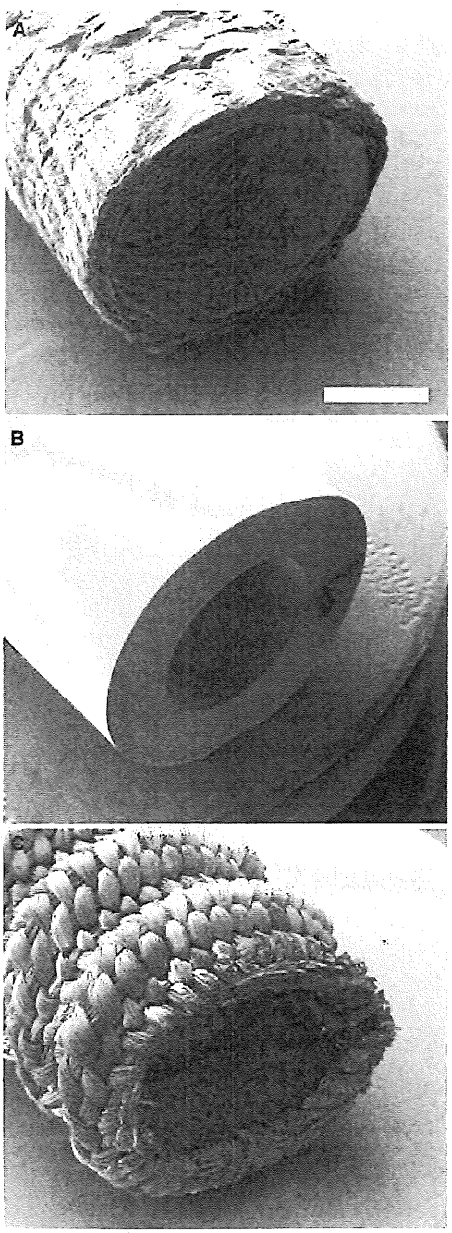

FIGURE 1. *Photographs demonstrating scanning electron micrographs of three types of nerve guides approved for clinical use.* A, *NeuraGen made from collagen.* B, *Neurolac made from polylactide/caprolacton.* C, *Neurotube made from polyglycolide.* Scale bar, *4 mm.*

ADVANCED NERVE GUIDE CONCEPTS

To date, all synthetic implants applied to humans are restricted in the sense that the implants only provide an initial mechanical scaffold. Thus, they meet the basic function of gross guidance between the proximal and distal nerve stump.

For defects limited to a few centimeters in length, self-regulatory biological mechanisms help to rebuild some sort of native neural cytoarchitecture. Approved nerve guides are available only for short defects. Longer defects need advanced implant concepts, which could only imply innovative material and biological science approaches.

Potential improvements in synthetic nerve guides could arise from advances in pliability, graded resorption along the longitudinal axis of the implant tube, chemically neutral hydrolysis of polymers, internal microstructuring reflecting the nerve fascicle architecture, and hydrophobic/hydrophilic surface coating of tubes to direct gliding of the implant along or integration into tissues. Further improvement may be expected from integrating more rigorously self-sustained biological components, such as specific cells that not only function as biofactories for growth factors but also respond to cell-cell signals that help to control (increase or decrease) factor synthesis. Such biohybrid implants with cells are likely to implement feedback systems that are automatically regulated by endogenous cell interactions.

Schwann cells are the most favored of such components because they aid axonal extension and neuronal survival, affect blood vessel formation, and possibly influence the embedding of connective tissue (44). Because procedures for the isolation of Schwann cells of lesioned nerves from human biopsies have been established (4), regeneration could possibly be greatly improved if autologous Schwann cells are incorporated into synthetic nerve guide implants. In animal models, Schwann cells seeded into synthetic nerve guides resulted in considerably better regeneration in the peripheral and the central nervous system (23, 46).

In lesioned nerves, Schwann cells form longitudinally oriented strands (bands of Büngner) that serve as a guiding rail for regrowing axons. We recently succeeded in recapitulating bands of Büngner in artificial nerve guides, preventing 1 μm thick axons from meandering aberrantly within a nerve guide with a cross-sectional diameter 1000 times larger. Schwann cells can be induced to form cell strands if they are seeded onto resorbable polymer filaments that have longitudinal grooves a few micrometers in width. Thus, the material topography leads to a longitudinal cell morphology that in turn results in cell-population structures reminiscent of bands of Büngner. Most intriguing is that this glial population structure can be used to enforce highly oriented axonal growth within nerve guides (22). Because microstructured polymer filaments can be produced as endless strings, a fairly straightforward concept for designing advanced nerve implants becomes feasible.

In summary, numerous studies indicate that short-distance defects in humans can be successfully treated by implantation of synthetic nerve guides. In the future, nerve guides might help to reduce the number of autologous nerve transplantations and the accompanying donor site morbidity. In addition, we expect progress in implant development because of interdisciplinary approaches that are searching the materials and life sciences for advances that could improve the neuro-tissue engineering needed to effectively treat larger nerve defects.

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COMMENTS

This study by Schlosshauer et al. is a comprehensive and thorough review detailing all published human studies using synthetic nerve guidance tubes in the clinical treatment of peripheral nerve injury. Their review provides a synthesis of clinical data, information and education as to the currently available human nerve guidance conduits, and a framework for future treatment of long defect nerve injury. This review will do more than just aid the practicing peripheral neurosurgeon. Indeed, the authors integrate experimental animal data in a "bench to bedside" translational approach, which will appeal to both the basic scientist and clinical investigator alike. Therefore, it nicely supplements previous reviews on the topic in which the experimental literature has been summarized (1).

The review correctly starts with a section on autologous nerve transplantation, detailing the current gold standard of treatment of nerve gaps that cannot be primarily repaired. Nerve autografts serve as an "ideal" conduit by providing a physiological scaffold and viable Schwann cells for regenerating nerve fibers and subsequent guidance of both sensory and motor axons to their appropriate targets (4). However, this method of nerve repair is limited because of donor site morbidity, a lack of donor tissue availability, incomplete and nonspecific regeneration, and subsequent poor recovery of function in both animal models and clinical cases. In addition, this biological constraint cannot be overcome by further progress in microsurgical technique. The authors address this issue, and emphasize that a synthetic nerve guide obviates the need for autografts, thereby overcoming the imposed limitations. An artificial or non-nerve conduit interposed between the proximal and distal stumps may also provide a more suitable environment for regenerating fibers to sample and respond to local environmental factors (2).

This review is a timely contribution to the literature, extending and updating the observation period of a similar review published by Meek and Coert in 2002 (5). It accounts for and summarizes all 23 published reports to date concerning nerve tubularization in humans, comprising data from more than 300 patients. *Table 1* provides a comprehensive list of the various case series and larger studies, the types of tubes used, the number of patients in each, and a summary of the findings.

This article recounts early pioneering studies reported in the late 1980s and early 1990s, in which Lundborg and colleagues demonstrated the feasibility and success of ulnar and median nerve reconstruction using short silicone conduits in six patients. However, both silicon and polytetrafluorethylene nerve guides are impermeable, non-biodegradable tubes, which elicit an inflammatory and fibrotic reaction and produce chronic nerve compression, resulting in their removal after regeneration had occurred through them. Investigators

have, therefore, increasingly used biodegradable materials for clinical use. Biodegradable tubes, such as those made from polyglycolic acid have led to a greater rate of successful functional recovery and have since been considered as equivalent to autologous nerve transplants for short gap (<3 cm) repairs (6). The article informs the reader about the five commercially available tubes (*Table 2*) for peripheral nerve reconstruction, including their associated material and degradation time. The authors acknowledge that these tubes are currently available exclusively for short defects. The article, therefore, argues strongly for the use of biodegradable nerve guides in short nerve defects, obviating the inherent problems of a nerve graft. In addition, the authors speculate about the potential future translational use of these tubes in other chronic debilitating neurological conditions such as spinal cord injury.

The final section of the review focuses on basic and advanced axonal guidance principles, which has been reviewed extensively elsewhere (3). The authors propose potential advancements in both tissue engineering and tube design, such as the administration of growth factors and implantation of Schwann cells, which may broaden their application to alleviate the deficits observed in long nerve injury gaps. Ultimately, through experimental animal work and early clinical trials, these principles will translate to a greater understanding of the exact mechanisms involved in peripheral nerve regeneration through conduits, and may eventually lead to the development of novel therapeutic interventions for improving outcome from nerve injuries.

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This article is a retrospective review of efforts to bridge peripheral nervous system gaps in patients by tubulization. The weaknesses of autologous grafting strategies, including donor site morbidity and limited supply, are introduced as motivation to devise a synthetic alternative to the common practice. Several categories of biomaterials are presented as options for the bridging tube. Non-biodegradable options, such as silicone tubes, have been largely discredited because they may compress the diametrically expanding nerve over time and cause pain or sensitivity. Biodegradable polymer (polyglycolic acid and polylactide-co-ϵ-caprolactone) tubes have been the most successful candidates for peripheral nerve repair thus far. The authors finish with a helpful discussion of the material properties of successful transplants. Overall, the article is well written and provides a good overview of the currently available synthetic nerve tubes in clinical use. The authors also provide a glimpse into the future of biocompatible nerve tubes, which may incorporate a variety of growth factors and cell regulatory systems to enhance nerve regeneration.

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Nerve guides, tubes, or conduits are increasingly being used in the repair of peripheral nerve defects. With this in mind, this review is a timely addition to the neurosurgical literature. The authors provide a nice overview of the reported clinical studies (and the context for them) on the use of non-biodegradable and biodegradable single lumen nerve tubes for peripheral nerve repair.

These first studies show that nerve conduits in selected situations may result in comparable functional outcome as those performed with an autologous nerve graft. However, care should be taken with the interpretation of these data or the extrapolation of them to the repair of larger nerves and/or larger nerve defects. As one can see tabulated in this article, biodegradable tubes have been used mostly in the repair of small nerve gaps (<3 cm) in small caliber sensory nerves, but not yet (with the exception of a rare case) in the repair of larger mixed or predominantly motor nerves innervating different distal targets.

Nevertheless, these first clinical results with "empty, hollow nerve tubes" reaffirm the results of earlier experimental work and encourage further research in advanced nerve guide concepts (e.g., multichannel structure and manipulation of the microenvironment with Schwann cells and neurotrophic factors, etc.). Optimizing the physical properties of the nerve tube (e.g., permeability, flexibility, swelling, and degradation) may also improve the results of regeneration; most of these properties are determined by the choice of biomaterial. As pointed out in this review, biodegradable materials are preferred because non-biodegradable, and perhaps also slowly biodegradable nerve tubes may cause local discomfort to the patient, making a secondary operation to remove the construct often necessary.

We think that the future of biodegradable nerve tubes is bright and that, with improved experience, energy, and engineering, we can demonstrate superior outcomes with nerve tubes and successfully build a better mouse trap.

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