Repair of Motor Nerve Gaps With Sensory Nerve Inhibits Regeneration in Rats

Michael J. Brenner, MD; Jason R. Hess, MD; Terence M. Myckatyn, MD; Ayato Hayashi, MD; Daniel A. Hunter, RA; Susan E. Mackinnon, MD

Objective: Sensory nerve grafts are often used to reconstruct injured motor nerves, but the consequences of such motor/sensory mismatches are not well studied. Sensory nerves have more diverse fiber distributions than motor nerves and may possess phenotypically distinct Schwann cells. Putative differences in Schwann cell characteristics and pathway architecture may negatively affect the regeneration of motor neurons down sensory pathways. We hypothesized that sensory grafts impair motor target reinnervation, thereby contributing to suboptimal outcomes. This study investigated the effect of motor versus sensory grafts on nerve regeneration and functional recovery. Study Design: The authors conducted a prospective, randomized, controlled animal study. Methods: Fifty-six Lewis rats were randomized to seven groups of eight animals each. Five-millimeter tibial nerve defects were reconstructed with motor or sensory nerve grafts comprised of single, double, triple, or quadruple cables. Tibial nerve autografts served as positive controls. Three weeks after reconstruction, nerves were harvested for histologic examination and quantitative histomorphometric analysis. Wet muscle masses provided an index of functional recovery. Results: Nerve regeneration was significantly greater across motor versus sensory nerve grafts independent of graft cross-sectional area or cable number. Motor grafts demonstrated increased nerve density, percent nerve, and total fiber number (P < .05). Normalized wet muscle masses trended toward improved recovery in motor versus sensory groups. Conclusions: Reconstruction of tibial nerve defects with nerve grafts of motor versus sensory origin enhanced nerve regeneration independent of cable number in a rodent model. Preferential nerve regeneration through motor nerve grafts may also promote functional recovery with potential implications for clinical nerve reconstruction. Key Words: Axon guidance, nerve regeneration, peripheral nerve, preferential motor reinnervation, nerve graft.


INTRODUCTION

Autologous nerve grafting is the preferred method for reconstructing nerve injuries in which a nerve gap precludes end-to-end repair. Typically, sensory nerve grafts such as the sural nerve or antebrachial cutaneous nerve are used to reconstruct motor defects because of their relative ease of harvest and low donor site morbidity. However, the assumption that motor grafts and sensory grafts are equally suitable substrates for motor regeneration has gone largely unchallenged. Attempts to restore useful function after nerve injury are often met with less-than-satisfactory results. For example, facial nerve reconstruction after facial nerve sacrifice seldom results in recovery better than a House-Brackmann grade III. It is possible that mismatch between motor nerve defect and sensory graft is a significant factor contributing to these often disappointing functional outcomes.

A growing body of literature addresses the role of motor and sensory pathways as determinants of axonal guidance and end-organ reinnervation.1-7 After nerve injury, motor axons preferentially regenerate down motor, rather than sensory, nerve branches to reach end targets. This phenomenon, termed preferential motor reinnervation, can be demonstrated even when neuronal contact with appropriate target motor and sensory end organs is prevented.2,3 If motor nerve tissue contains signals specific to motor axonal guidance, then interposition of sensory nerve grafts may result in an inhospitable environment. Mismatch between nerve graft and nerve defect may thus predispose to impaired regeneration, ultimately contributing to unsatisfactory functional outcomes.

We have previously described reconstruction of a tibial nerve defect with motor versus sensory derived nerve tissue.8 This work demonstrated that nerve regeneration was more robust when nerve defects were reconstructed with motor rather than sensory-derived nerve grafts. How-
ever, a difference in graft architecture introduced potential sources of confounding. The present study tested the hypothesis that motor graft composition was associated with enhanced neuroregeneration independent of the number of cable grafts used and graft cross-sectional area.

MATERIALS AND METHODS

Animal Care

All interventions were performed in strict accordance with the National Institutes of Health guidelines. The experimental protocol was approved by the Washington University Animal Studies Committee before initiation of the project. Adult male Lewis rats (Harlan Sprague-Dawley, Indianapolis, IN) weighing 250 to 350 g were quarantined and subsequently housed in a central animal care facility. All animals were provided a 12-hour light/dark cycle and given a rodent balanced diet (Pico Lab Rodent Diet #20 #5053; PMI Nutrition International) in addition to water ad libitum. After surgical procedures, the animals were recovered in a warm environment and closely monitored for 3 hours. Animals were then returned to the animal care facility and examined daily for weight loss, signs of infection, excessive pain, or other morbidity.

Experimental Design

A total of 56 rats were randomized to seven groups of eight animals each as shown in Table I. An additional 25 animals served as nerve graft donors. In all experimental animals, a 5-mm tibial nerve gap was created and immediately reconstructed with a nerve graft of equivalent length. Experimental groups were defined based on the number and composition (motor or sensory) of cable grafts used for reconstruction. Nerve grafts were harvested from the distal motor and sensory branches of the femoral nerve. Motor nerve grafts were derived from the femoral motor branch to the quadriceps, and sensory nerve grafts were derived from the femoral saphenous branch. Corresponding quantitative data from representative donor motor and sensory nerves are shown in Table II.

Animal in group I served as positive controls and received a reversed tibial nerve autograft. Animals in group II received a single-cable motor isograft. Animals in group III received a double-cable motor isograft, which resulted in a cross-sectional area that was similar to the recipient stump. Animals in group IV received a triple-cable motor graft which, in total, was larger than the tibial nerve stumps. Animals in group V received a single-cable sensory graft. Animals in group VI received a triple-cable sensory graft, which was roughly equivalent in cross-sectional area to the recipient nerve ends. Last, group VII animals received four sensory cables, which created a larger cross-sectional area.

Fig. 1. Gross appearance of cable grafts. (A) Single sensory nerve graft. (B) Triple sensory nerve graft. (C) Quadruple sensory nerve graft. (D) Triple motor nerve graft bridging a 5-mm tibial nerve defect. Use of a triple sensory nerve graft resulted in an optimal size match between proximal and distal nerve stumps, similar in appearance to double motor nerve graft (picture not shown). The quadruple sensory and triple motor grafts result in a graft that is wider in caliber than the native nerve.

### TABLE I. Experimental Design.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Graft Type</th>
<th>Cables</th>
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<tr>
<td>Group I</td>
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<td>Tibial</td>
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</tr>
<tr>
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<td>Group IV</td>
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<td>Motor</td>
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</tr>
<tr>
<td>Group V</td>
<td>8</td>
<td>Sensory</td>
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</tr>
<tr>
<td>Group VI</td>
<td>8</td>
<td>Sensory</td>
<td>3</td>
</tr>
<tr>
<td>Group VII</td>
<td>8</td>
<td>Sensory</td>
<td>4</td>
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</tbody>
</table>

### TABLE II. Comparison of Representative Motor and Sensory Donor Nerves Used for Nerve Reconstruction.*

<table>
<thead>
<tr>
<th>Fiber Count</th>
<th>Nerve Area (μm²)</th>
<th>Fiber Width (μm)</th>
<th>Nerve Density (fibers/mm²)</th>
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<tbody>
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<td>Motor</td>
<td>638</td>
<td>63,853</td>
<td>6.08</td>
</tr>
<tr>
<td>Sensory</td>
<td>1213</td>
<td>55,057</td>
<td>4.87</td>
</tr>
</tbody>
</table>

*Motor nerve grafts were derived from the femoral nerve branch to the quadriceps. Sensory nerve grafts were derived from the cutaneous sensory branch of the femoral nerve.
than the recipient stumps. Animals were killed at a 3-week end point, and the nerve tissue was harvested for standard histomorphometric analysis. The bilateral gastrocnemii were also harvested for wet weight ratios as a measure of functional recovery for animals in groups I (control), III (double-cable motor), and VI (triple-cable sensory) because these three groups represented grafts of approximately similar caliber.

Surgical Techniques

All surgical procedures were performed under general anesthesia. This was achieved by intramuscular injection of 75 mg/kg ketamine (Fort Dodge Animal Health, Fort Dodge, IA) in combination with 0.5 mg/kg medetomidine (Orion Corporation, Espoo, Finland). Each animal’s right hindquarter was shaved, prepped with Betadine solution, and draped in standard aseptic fashion.

For donor nerve harvests, a no. 15 scalpel blade was used to create an oblique cutaneous groin incision extending from the minguinal ligament to the medial popliteal region. The saphenous branch of the femoral nerve was then identified at its branch point from the femoral nerve with the aid of the Wilde M651 operating microscope (Leica Microsystems, Deerfield, IL) under 16× magnification. With 25× magnification, the nerve was then neurolysed, resected, and divided into 5-mm segments for later use as sensory cable graft segments.

Motor graft harvests were also performed using this incision. The motor branch to the quadriceps was identified under 16× magnification at its branch point from the femoral nerve. Under 25× magnification, the nerve was neurolysed, resected, and divided into 5-mm cables. All donor animals were killed by intracardiac injection of 1 mL Euthasol (Delmarva Laboratories, Des Moines, IA), which was administered while animals were under general anesthesia.

In the recipient animals, the tibial nerve was approached through a 15-mm incision extending from just behind the sciatic notch to the superior popliteal region distally. A gluteal muscle-splitting incision was used to expose the sciatic nerve. The nerve was then neurolysed to the area of the sciatic trifurcation where the tibial branch was identified and isolated from the neighboring sural and peroneal nerves. Microscissors were used to resect a 5-mm segment from the tibial nerve beginning approximately 4 mm distal to the trifurcation.

In control animals, a 5-mm segment of the tibial nerve was resected, reversed, and secured within the gap using four 11-0 microsutures placed at each end under 40× magnification. These epineural sutures were placed equidistant from one another. In the sensory nerve graft groups, 5-mm grafts consisting of one, three, or four cables were used to bridge the gap. Two to three 11-0 nylon microsutures were used to attach each cable end to the divided tibial stumps. In the motor nerve graft groups, repairs consisted of one, two, or three cable motor grafts bridging the gap in a similar fashion. To minimize trauma to stacked grafts, a single 11-0 nylon rosette stitch was used to bind grafts at each end. The gross appearance of cable grafts for all sensory nerve grafts as well as the triple-cable motor graft motor group is shown in Figure 1.

While still anesthetized, animals were administered subcutaneous injections of 0.01 to 0.05 mg/kg Buprenex for analgesia. Anesthesia in experimental animals was then reversed with 0.2 mg/kg intramuscular injection atipamezole HCl (Pfizer Animal Health, Exton, PA). Postoperative recovery was performed in a warmed aseptic environment, and animals were returned to the housing facility when ambulatory and demonstrating appropriate oral intake.

At the 3-week end point, all animals were subjected to general anesthesia as previously stated and the bilateral hindlimbs were shaved, prepped, and draped as described previously. The right tibial nerve was approached as described. In all experimental animals, the graft was neurolysed and resected with microscissors to include the tibial nerve 3 mm proximal and at least 5 mm distal to the graft region. The tissue was then placed in 3% glutaraldehyde and stored at 4°C before histomorphometric analysis.

Bilateral gastrocnemii were surgically approached using a posterior tibial incision. Under 6× magnification, these muscles were divided from surrounding tissue, resected, and weighed using an analytical balance. The wet weight ratio between experimental (right) and control (left) sides was measured. The anesthetized animals were then sacrificed as described.

Histomorphometric Analysis

After overnight fixation in cold, buffered 3% glutaraldehyde, nerve specimens were postfixed in 1% osmium tetroxide and dehydrated in graduated ethanol concentrations (50%, 70%, 90%, and 100%). The tissue was then imbedded in Araldite 502 (Polysciences, Warrington, PA). An LKB III Ultramicrotome (LKB-Produkter, Sweden) was used to create cross-sections of 1-µm thickness. Sections were stained with 1% toluidine blue and viewed under light microscopy. A digital image analysis system was used to analyze the images with the assistance of linked morphometry software (Leco Instruments, St. Joseph, MI).

Light microscopic images were then converted to digital images and six randomly selected fields, each measuring 5.5 × 10^3 μm², were evaluated using eight-bitplane digital pseudocoloring and gray scale-based algorithms to differentiate neural architecture, including myelin, neural debris, blood vessels, and axons. A distinct bitplane was assigned to each component of neural architecture, including total fascicular area, axon counts, area, width, and myelin thickness, and real-time measurements and calculations of these parameters were performed. Then, axon counts were stratified as histograms characterized by axonal area, width, and myelin thickness. These measurements were then used in the calculation of total neural tissue percentage (100 × neural area/intrafascicular area), neural debris (100 × neural debris/intrafascicular area), nerve fiber density (fibers/mm²), and the total number of myelinated fibers.

For electron microscopy, ultrathin 90-nm sections of the embedded tissues were prepared with the aid of the LKB III microtome and stained with uranyl acetate–lead citrate. These sections were examined under a Zeiss 902 electron microscope (Zeiss Instruments, Chicago, IL). Quality of myelination, relative prevalence of unmyelinated fibers, and presence or absence of Wallerian degeneration were evaluated.

Statistical Analysis

All results are reported as mean ± standard deviation unless noted otherwise. Statistical analysis was performed using Statistica version 6 (Statsoft Inc., Tulsa, OK). Means for histomorphometry data and wet muscle masses were evaluated using analysis of variance (ANOVA). For histomorphometric data, a post hoc Newman-Keuls test was used for comparison of differences between groups with significance set at P < .05.

RESULTS

All animals enrolled in the study survived to the 3-week end point. There were no obvious signs of infection or undue morbidity within the study population. All animals exhibited appropriate weight gain, and all microsurgical repairs were intact at the time of harvest.

Histology

Qualitative examination of the midgraft and distal nerve segments revealed robust regeneration across control and motor nerve grafts when compared with sensory

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nerve graft groups. Cross-sections taken at midgraft and distal to sensory grafts were characterized by a relative paucity of regenerating fibers and markedly increased neural debris. Regardless of the number of cables grafted, motor grafts yielded nerve fibers with increased maturity as reflected in myelin thickness and fiber width. Fibers were more densely packed in motor groups. Low- and high-magnification comparisons are shown for the triple motor and the triple sensory grafts in Figure 2. Representative histology for distal nerve for the triple-cable motor and triple-cable sensory groups is shown in Figure 3.

**Histomorphometry**

The examined parameters of nerve regeneration within the grafts included nerve fiber counts, fiber density, fiber width, percent nerve, and percent debris. At 3 weeks, nerve regeneration within the mixed nerve control group and motor isografts was robust for all measured parameters. Total fiber number, density, and percent nerve across all motor groups were similar to control grafts. Comparisons between single-cable and triple-cable motor grafts and all sensory graft groups demonstrated significantly improved regeneration in the motor group as measured by total fiber number, nerve density, and percent nerve (all \( P < .05 \)). As the number of sensory nerve cables grafted into the defect increased, the difference in regeneration between motor and sensory grafts increased, with fiber count, percent nerve, nerve width, and nerve density all uniformly trending downward (Fig. 4). Impaired regeneration in the sensory group was associated with significantly increased neural debris in the four-cable sensory graft group relative to all other experimental groups (\( P < .05 \)).

**Electron Microscopy**

Electron microscopy demonstrated multiple regenerating units in various stages of maturity, as reflected by fiber diameter and myelin thickness (Fig. 5). As noted on light microscopy, more regenerating fibers were present in motor and control groups (groups I–IV) than in the sensory cable groups (groups V–VII). Both myelinated and unmyelinated neurons were more prevalent in groups I through IV. Myelin thickness and fiber diameter were mildly increased in the motor and control groups as compared with the sensory groups by comparison of random cross-sections distal to the grafts.

**Wet Muscle Mass Analysis**

Gastrocnemius wet muscle masses were markedly diminished on the operated side in the three groups studied, consistent with only minimal reinnervation at the relatively early 3-week experimental end point. Differences between groups were not statistically significant.

**DISCUSSION**

The seminal experiments on preferential motor reinnervation\(^1\)–\(^4\),\(^6\) emphasize the key roles that motor and sensory pathways play in modulating axonal guidance. The majority of these studies were performed in small animal models in which the femoral nerve was transected proximal to its bifurcation into motor and sensory branches. In these experiments, regenerating neurons from the mixed proximal nerve stump were provided access to distal motor or sensory branches, usually using a Y-shaped conduit.\(^1\),\(^3\),\(^4\) The predilection of motor nerves for motor pathways has proven a robust and reproducible phenomenon.
These prior experiments cannot be directly extrapolated to autologous nerve graft reconstruction for a few reasons, however. First, in the classic femoral nerve preparation, regenerating axons have equal access to both motor and sensory pathways; in autologous nerve graft reconstruction, the selection of motor or sensory pathway is determined by the surgeon. Second, conduits provide a synthetic microenvironment with characteristics that differ from epineurial suture repair. Conduits may artificially enrich for neurotrophins, induce inflammation, or otherwise alter the dynamics of nerve regeneration. It is therefore difficult to predict the consequences of “forcing” motor neuron regeneration down a sensory pathway as occurs in the routine practice of grafting autologous sensory nerves into motor nerve defects.

The present study establishes that nerve grafts of motor origin will support regeneration across a predominantly motor defect more effectively than will sensory nerve grafts. Building on our prior work showing benefit with motor versus sensory grafting,8 the present study demonstrates that this phenomenon is independent of manipulation of graft caliber and fascicular content. The close concordance in regeneration between the positive control group (tibial nerve graft) and all of the motor cable graft groups underscores the primacy of compositional factors over technical factors. The underlying mechanisms may involve production of growth factors, extracellular matrix signals, or exposure to motor-associated Schwann cells.

The use of electron microscopy helped to confirm preferential regeneration across motor nerve grafts. Ultrastructural analysis allowed for assessment of unmyelinated and myelinated nerve fibers. Ratios of these fibers were similar across groups. This finding is significant because it excludes the possibility that differences between motor and sensory nerve grafts arose solely from an increase in nonmyelinated fibers in the sensory graft.

In this experiment, sensory nerve grafts appeared to actively inhibit motor neuronal growth. As the number of sensory nerve cable grafts increased, the distal fiber counts dropped, with similar findings noted for percent neural tissue and neural density. This pattern was not observed in the motor nerve graft groups. The increased neural debris in the sensory pathway group reflects impaired clearance of residual breakdown products of Wallerian degeneration. This retarded degradation of myelin and axonal breakdown products is a common feature of nerve grafts with impaired regeneration and is a harbinger of compromised end-organ reinnervation.

When regenerating motor neurons encounter sensory nerve grafts, they will not encounter motor Schwann cell tubules. This may retard regeneration. A neuronal growth cone will proceed down a Schwann cell tube only when attraction outweighs inhibition. Axons may migrate laterally across the face of a nerve stump, often interacting with over 100 Schwann cell tubes.9 Axonal arborization facilitates interactive sampling of available Schwann cell tubules, but neurons with larger arborization may be at a competitive disadvantage when reinnervating muscle fibers. In our experiment, increasing the number of sensory nerve cables may have increased the magnitude of contact repulsion or chemorepulsion.

For motor and sensory pathways to differentially regulate axonal guidance, they must possess distinct biochemical properties. One candidate signal is carbohydrate L2/HNK-1, which is preferentially expressed on Schwann cells associated with motor neurons.10 Motor neurite outgrowth is enhanced in medium containing this marker, and this neurone Enhancement is abolished with addition of antibodies directed against this marker. Expression of L2/HNK-1 is elevated when motor neurons enter a motor graft and depressed when motor neurons enter a sensory nerve graft. Furthermore, motor Schwann cells maintain L2/HNK1 expression, and hence their motor identity, even after the axon they originally myelinated has undergone Wallerian degeneration. These findings suggest that Schwann cells are not passive partners in axon–Schwann cell relationships.

A handful of prior studies have considered the effects of motor and sensory graft composition on subsequent nerve regeneration.4,8,11–13 One study examined facial

Fig. 3. Representative toluidine blue-stained histologic sections taken distal to nerve grafts are shown for (A) triple-cable motor graft and (B) triple-cable sensory graft. The three motor graft groups all had similar appearance with robust nerve regeneration independent of cable number. All sensory cable graft groups had far fewer fibers with nerve regeneration decreasing as cable number increased. Virtually no regeneration is present in the quadruple-cable sensory group (not shown).
nerve repair in a rabbit model using 1-cm great auricular nerve or facial nerve grafts. Unfortunately, electroneurographic and histologic studies were not performed until 21 to 24 weeks. Such late time points preclude meaningful interpretation of differences in small animal models, particularly when short nerve gaps are under study. Functional differences were not noted between groups. Data from our prior research study, in which cable grafting was used, more clearly showed a beneficial effect of motor grafts on nerve regeneration.8 However, in this preliminary study, only two experimental groups in addition to the positive control were included. Therefore, it was possible that differences in the grafted groups arose from technical differences in the repairs, variation in fascicular count, or compositional differences.

In the rodent model proposed by Ghalib et al., sensory or motor nerve branches derived from the femoral nerve were grafted into a defect in the quadriceps branch of the femoral nerve.11 The authors found that fibers distal to the motor graft were characterized by a larger-diameter and greater myelin thickness than those from the sensory graft at the 14-day end point. The authors concluded that extracellular matrix factors accounted for improved maturation of motor fibers within the motor versus cutaneous graft.11 No functional outcomes were reported with this study. Two additional studies4,5 examined the outcome

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**Fig. 4.** Histomorphometric comparisons of nerve regeneration across control, motor, and sensory groups of varying cable number. Total fiber number, density, and percent nerve in all motor groups were equal to control tibial nerve grafts. Mean fiber counts were increased in all comparisons of motor-grafted groups compared with sensory-grafted groups \((P < .05)\). Motor versus sensory comparisons for percent neural tissue and nerve density were significant in all comparisons except the double motor graft group, which showed a parallel trend \((P < .05)\). Increased neural debris in the quadruple sensory graft group relative to other sensory graft groups \((P < .05)\) was associated with trends toward decreased fiber width, fiber count, neural density, and percent neural tissue.
when a femoral nerve and its distal motor and sensory nerve branches were grafted into a Y-shaped defect. The results suggested that preferential motor reinnervation is relevant to nerve grafting as well as crush/transection models. Because regenerating nerves were provided access to both motor and sensory pathways, the implications of these latter studies for autologous grafting are unclear.

The present experiment was carefully designed to control for potentially confounding effects of differing fascicle number, fiber count, nerve cross-sectional area, and donor–recipient nerve size match. The large number of comparisons in our study allowed for identification of a dose-related inhibitory effect of sensory nerve grafts not previously described. This approach also allowed for a far more compelling demonstration of the beneficial effect of motor nerve grafting than was possible in earlier work. It is interesting to note that the absolute values for several indices of regeneration, including fiber count, density, and percent neural tissue, were higher in the present study than in previous work. This finding reflects the significant variability encountered in study of peripheral nerve regeneration. It also underscores the importance of including concurrent rather than historical controls in scientific investigations.

Prior experience has suggested that nerve regeneration is most robust when graft caliber and axonal density matches that of the recipient nerve defect. However, in the present study, there was no effect of number of cable grafts on regeneration in the motor graft group. This finding suggests that motor/sensory composition is a more important determinant of regenerative capacity than the physical constraints of graft configuration. In support of this observation is a prior study using single fascicular grafting that suggested no impairment in regeneration with this approach.

We have previously shown that nerve regeneration is also not significantly affected by the geometry of the nerve repair. These findings are of interest because peripheral nerve surgeons often stack small donor nerves together when repairing defects in large recipient nerves in an effort to improve size match. The present study supports the role of motor/sensory pathways as a determinant of nerve regeneration. Although sensory nerves are more readily expendable than their motor counterparts, the routine practice of using sensory nerve grafts to reconstruct motor nerve defects may warrant reappraisal. Motor nerves to the latissimus, rectus, medial, or lateral gastrocnemius, motor nerve of the vastus lateralis, and gracilis are among the candidate donor nerves that might be harvested with acceptable morbidity. Donor site morbidity and available length of nerve tissue will be important considerations in the potential use of motor nerve grafts in motor defects. Although preliminary work does suggest that preferential motor reinnervation is conserved in primates, further experiments investigating functional outcomes in large animal models are needed. Long-term strategies may include use of motor nerve allografts or development of tissue engineered conduits containing motor-derived Schwann cells.

CONCLUSION

Use of motor or mixed nerve grafts, rather than sensory nerve grafts, improved regeneration across a predominantly motor nerve defect in a rodent model. This differential effect was conserved across experimental groups,
independent of differences in fascicle count or graft caliber. These data suggest that neurobiologic influences are more significant than mechanical properties for determining outcome after nerve reconstruction. Further investigation is needed to determine whether the benefits of grafting motor or mixed nerve into motor neuron lesions are sufficient to justify an increase in associated donor site morbidity.

**BIBLIOGRAPHY**