ELECTRICAL STIMULATION IN MUSCLE REINNERVATION

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Al Majed A.A., Neumann C.M., Brushart T.M., and Gordon T. (2000) Brief electrical stimulation promotes the speed and accuracy of motor axonal regeneration. J. Neurosci. 20, 2602-2608.
Abstract: Functional recovery is often poor despite the capacity for axonal regeneration in the peripheral nervous system and advances in microsurgical technique. Regeneration of axons in mixed nerve into inappropriate pathways is a major contributing factor to this failure. In this study, we use the rat femoral nerve model of transection and surgical repair to evaluate (1) the effect of nerve transection on the speed of regeneration and the generation of motor-sensory specificity, (2) the efficacy of electrical stimulation in accelerating axonal regeneration and promoting the reinnervation of appropriate muscle pathways by femoral motor nerves, and (3) the mechanism of action of electrical stimulation. Using the retrograde neurotracers fluorogold and fluororuby to backlabel motoneurons that regenerate axons into muscle and cutaneous pathways, we found the following. (1) There is a very protracted period (10 weeks) of axonal outgrowth that adds substantially to the delay in axonal regeneration (staggered regeneration). This process of staggered regeneration is associated with preferential motor reinnervation (PMR). (2) One hour to 2 weeks of 20 Hz continuous electrical stimulation of the parent axons proximal to the repair site dramatically reduces this period (to 3 weeks) and accelerates PMR. (3) The positive effect of short-term electrical stimulation is mediated via the cell body, implicating an enhanced growth program. The effectiveness of such a short-period low-frequency electrical stimulation suggests a new therapeutic approach to accelerate nerve regeneration after injury and, in turn, improve functional recovery

Andreose J.S., Xu R., Lomo T., Salpeter M.M., and Fumagalli G. (1993) Degradation of two AChR populations at rat neuromuscular junctions: regulation in vivo by electrical stimulation. J. Neurosci. 13, 3433-3438.
Abstract: The effect of electrical stimulation on the stability of junctional ACh receptors (AChR) on soleus muscles of Wistar rats was compared to that of denervation and reinnervation. Denervation causes the degradation rate of the slowly degrading AChRs (Rs) at the neuromuscular junction to accelerate and be replaced by rapidly degrading AChRs (Rr), while reinnervation restabilizes the accelerated Rs. Electrical stimulation initiated at the time of denervation prevented the acceleration of the Rs. It could not, however, reverse the effect of denervation if initiated after the AChRs became destabilized, nor could it slow the degradation rate of the Rr. We conclude that electrical stimulation of denervated muscle downregulates the expression of the Rr and prevents the destabilization of Rs

Angaut-Petit D. and Mallart A. (1985) Electrical activity of mouse motor endings during muscle reinnervation. Neuroscience 16, 1047-1056.
Abstract: An in vitro study of electrical activity of regenerating motor endings was performed 11-15 days after the crushing of one motor nerve supplying the triangularis sterni muscle in the adult mouse. For this purpose, presynaptic membrane currents elicited by electrical stimulation of the regenerating nerve were recorded by external electrodes. Ionic channel distribution along the length of the endings was deduced from wave form configuration in normal perfusing fluid together with changes produced by application of specific channel blocking agents. The sharp negative deflection which was shown to correspond to inward Na+ current

by its sensitivity to tetrodotoxin application could be recorded along most of the length of the endings indicating a widespread distribution of Na channels. Frequent absence of the late wave form component which signals K+ current was taken to indicate an even K+ current density in the few last nodes, the heminode and the distal part of the endings. Therefore, it appears that regenerating motor endings are characterized by an overlap of Na and K conductances all along their length. In the course of regeneration, the heminode loses the sensitivity to K channel blocking agents and the remainder of the terminal becomes insensitive to tetrodotoxin, the former change occurring usually earlier than the latter

Anonsen C.K., Patterson H.C., Trachy R.E., Gordon A.M., and Cummings C.W. (1985) Reinnervation of skeletal muscle with a neuromuscular pedicle. Otolaryngol. Head Neck Surg. 93, 48-57.
Abstract: In the past decade the otolaryngologist has become interested in the problem of muscle reinnervation as it relates to laryngeal and facial paralysis. Although reinnervation by neuromuscular pedicle transfer has shown promising results in the laboratory and clinic, some investigators have had difficulty in achieving reliable results with this procedure. To further assess the technique's validity, we investigated the neuromuscular pedicle. This study utilized a strap muscle neuromuscular pedicle transfer to a contralateral strap muscle in the rabbit. The results were analyzed by the use of a number of independent measures, including electrical stimulation of the nerve, muscle contractibility, electromyography, enzyme histochemistry, reduced-silver staining for normal fibers, and the retrograde transport of the enzyme marker horseradish peroxidase. The physiologic and anatomic results demonstrated that morphologic and functional reinnervation of the experimentally isolated muscle by the transferred neuromuscular pedicle occurred. The most convincing data were produced by gross electrical stimulation, twitch and tetanic contraction, and horseradish peroxidase labeling. Electromyographic activity and other histologic findings supported the above conclusions

Bacou F., Rouanet P., Barjot C., Janmot C., Vigneron P., and d'Albis A. (1996) Expression of myosin isoforms in denervated, cross-reinnervated, and electrically stimulated rabbit muscles. Eur. J. Biochem. 236, 539-547.
Abstract: The expression of myosin heavy (MyHC) and light (MyLC) chain isoforms was analyzed after denervation and cross-reinnervation by a fast nerve of the slow-twitch Semimembranosus proprius (SMp) muscle, and after denervation and electrical stimulation at low frequency of the fast- twitch Semimembranous accessorius (SMa) muscle of the rabbit. The control SMp (100% type I fibers) expressed 100% type I MyHC and 100% slow-type (1S', 1S and 2S) MyLC isoforms. Five month denervation did not alter significantly the MyHC expression of the muscle, but induced the expression of a new type 1 MyLC corresponding most probably to an embryonic MyLC. Five-month cross-reinnervation of the SMp by the fast SMa nerve induced a large change of its fiber type properties. As shown by immunocytochemistry, almost all fibers were stained by fast myosin antibody, but a high proportion of them co-expressed slow myosin. This result was in agreement with biochemical data showing that fast MyHC and MyLC isoforms became predominant. The control SMa (nearly 100% type II fibers) expressed almost 100% type II MyHC (70% type IIb and 22% IIx/d) and 100% fast-type (1F, 2F and 3F) MyLC isoforms. Five month denervation of the SMa induced a shift in its MyHC, with 98% type IIx/d and 2% type IIb isoforms, and no change in the proportions of its MyLC. Three month electrical stimulation at 10 Hz of the SMa transformed its fiber

type composition. All fibers reacted with the slow myosin antibody and a minor proportion of them were stained by the fast myosin antibody. These observations were in agreement with the biochemical analysis showing a large predominance of the slow-type MyHC and MyLC isoforms. Taken together, these results obtained from rabbit muscles which are normally homogeneous in either fast-twitch or slow-twitch fiber types, further support the idea that the different myosin isoforms, particularly the MyHC, are differentially regulated by motor innervation. Type I MyHC is maintained in denervated SMp muscle, but is not expressed in denervated SMa. Type IIb isoform is the most sensitive to neural influence, as it disappears rapidly in denervated and electrically stimulated fast-twitch SMa muscle, and is barely expressed in cross-reinnervated slow-twitch SMp muscle. In contrast, type IIa and type IIx/d are less dependent upon motor innervation. In addition to the previous studies of d'Albis et al. analysis of these results leads us to conclude that, in the rabbit, sensitivity to motor innervation increases from the glycolytic to the oxydative types of fibers, in the order IIB > IIX/IID > IIA > I

Badke A., Irintchev A.P., Wernig A. (1989) Maturation of Transmission in Reinnervated Mouse Soleus Muscle. *Muscle & Nerve* 12:580-586.
Abstract: After the tibial nerve of the mouse was cut unilaterally and immediately re-sutuared, reinnervation of soleus muscle proceeded rapidly and muscle isometric contraction characteristics reached normal values within 2 months. In contrast, synaptic transmission remained immature since resistance to pre-synaptic (magnesium) or post-synaptic (curare) blocking solutions remained reduced. Results suggest that release probability and transmitter stores were smaller than normal. To study the effect of training, animals were allowed to run in wheels. Running caused a delay in reinnervation at 18-20 days, which was, however, abolished by 4 weeks. On the other hand, exercise counteracted development of denervation atrophy. The safety margin of transmission in runners was higher than in nonrunners at 4 weeks, indicating enhanced maturation, but was lower at 2 months of reinnervation. These results suggest that recovery of muscle precedes maturation of synaptic transmission.

Becker M.H., Lassner F., Dagtekin F.Z., Walter G.F., and Berger A. (1995) Morphometric changes in free neurovascular latissimus dorsi flaps: an experimental study. Microsurgery 16, 786-792.
Abstract: This study was designed to investigate regeneration of reinnervated, free transplanted muscles. We used a rat model, consisting of eight rats per group, in which the latissimus dorsi muscle was transplanted orthotopically and then harvested and evaluated after 2 and 12 weeks. Age-matched control animals were used to oppose non-operated muscles. At date of removal the patency of the vascular anastomoses was checked clinically and histologically. Electrophysiological measurements were also performed and conventional and enzyme histochemical histological slides manufactured. Two weeks after the free neurovascular flap transfer the muscle was not yet innervated, and histologically a dissolved pattern of type 1 and type IIA muscle fibres was found. The muscle fibres demonstrated a decrease of more than 50% cross-sectional area. After 12 weeks the muscles were reinnervated again; muscle contraction was positive with electrical stimulation and the cross- sectional area had regained 80% of the activity of normal muscle fibres. With enzyme histochemical staining the typical type grouping of reinnervated muscles could be demonstrated

Becker M.H., Lassner F., Dagtekin F., Walter G.F., and Berger A. (1995) [Muscle-specific changes in free latissimus dorsi transplantation in the rat model]. Handchir. Mikrochir. Plast. Chir 27, 93-97.
Abstract: The aim of this study is to gain further knowledge concerning the regeneration of reinnervated, freely transplanted muscles. Therefore, we used a rat model, consisting of eight rats per group, in which the latissimus dorsi muscle was transplanted orthotopically, after a period of time of two and twelve weeks harvested, then evaluated histologically and enzyme-histochemically. As controls we used a group of non-operated muscles. At date of removal, the patency of the vascular anastomoses was checked clinically and histologically. Additionally, electrophysiological measurements and conventional and enzyme-histochemical histologies were performed. Two weeks after the free neurovascular flap transplantation, the muscle was not innervated yet, histologically a dissolved pattern of type 1 and type 2 muscle fibers was found. After twelve weeks of time, the muscles were reinnervated again, muscle contraction was positive

Bennett R.L., Knowlton G.C. (1958) Overwork weakness in partially denervated skeletal muscle. *Clin Orthop* 12, 22-29.

Bensman A. (1970) Strenuous exercise may impair muscle function in Guillain-Barre patients. *JAMA* 214:468-469.

Blaskey J, Broder C, Montgoamery J, Parker K, Pohl P (1986) *Therapeutic Management of Patients with Guillain-Barre Syndrome.* Professional Staff Association of Rancho Los Amigos Medical Center, Inc., Downey, CA.

Bowen J.M. (1977) Denervation in the Canine Pectineus Muscle: Quantitative EMG Analysis of Its Time Course. *Arch Phys Med Rehabil* 58, 339-344.

Chamberlain L.J., Yannas I.V., Hsu H.P., Strichartz G.R., and Spector M. (2000) Near-terminus axonal structure and function following rat sciatic nerve regeneration through a collagen-GAG matrix in a ten-millimeter gap. J. Neurosci. Res. 60, 666-677.
Abstract: The objectives of this study were to evaluate the regenerated axon structure at near-terminal locations in the peroneal and tibial branches 1 year following implantation of several tubular devices in a 10-mm gap in the adult rat sciatic nerve and to determine the extent of recovery of selected sensory and motor functions. The devices were collagen and silicone tubes implanted alone or filled with a porous collagen-glycosaminoglycan matrix. Intact contralateral nerves and autografts were used as controls. Nerves were retrieved at 30 and 60 weeks postoperatively for histological evaluation of the number and diameter of regenerated axons proximal and distal to the gap and in the tibial and peroneal nerve branches, near the termination point. Several functional evaluation methods were employed: gait analysis, pinch test, muscle circumference, and response to electrical stimulation. A notable finding was that the matrix-filled collagen tube group had a significantly greater number of large-diameter myelinated axons (> or =6 microm in diameter) in the distal nerve branches than any other group, including the autograft group. These results were consistent with previously reported electrophysiological measurements that showed that the action potential amplitude for the A fibers in the matrix- filled collagen tube group was greater than for the autograft control group. Functional testing revealed the existence of both sensory and motor recovery

following peripheral nerve regeneration through all devices; however, the tests employed in this study did not show differences among the groups with regeneration. Electrical stimulation in vivo showed that threshold parameters to elicit muscle twitch were the same for reinnervating and control nerves. The investigation is of importance in showing for the first time the superiority of a specific fully resorbable off-the-shelf device over an autograft for bridging gaps in peripheral nerve, with respect to the near-terminus axonal structure

Cole B.G. and Gardiner P.F. (1984) Does electrical stimulation of denervated muscle, continued after reinnervation, influence recovery of contractile function? Exp. Neurol. 85, 52-62.
Abstract: The study was conducted to determine if daily electrical stimulation of denervated muscle, initiated the day following crush denervation and continued for 8 weeks (i.e., 5 weeks after presumptive reinnervation), would influence denervation-associated alterations in muscle size and in situ contractile properties of rat gastrocnemius. A stimulation protocol of brief, strong, isometric contractions was designed to maximize the beneficial effects as described by previous authors. By 8 weeks after crush, unstimulated muscles were still significantly lighter in wet weight, were tetanically weaker, and showed slower isometric contractile responses in situ than controls. Denervated muscles which had been stimulated daily were heavier and tetanically stronger (the latter not different from controls) than those in the nonstimulated group. Muscle weights from groups of animals killed at 2 or 4 weeks after nerve crush indicated the major benefit of stimulation occurred during this initial 4-week period. In situ fatigue properties were unaffected by denervation or stimulation. A protocol of electrical stimulation-evoked strong contractions, initiated soon after denervation and continued after reinnervation, was effective in attenuating the strength-related, but not speed-related, changes in neuromuscular function resulting from denervation. These latter changes are presumably the result of loss of "neurotrophic influence" and/or continuous low-tension muscle activity lost as a result of denervation

Cope T.C., Bonasera S.J., and Nichols T.R. (1994) Reinnervated muscles fail to produce stretch reflexes. J. Neurophysiol. 71, 817-820.
Abstract: 1. We studied the stretch-evoked reflex organization of hind limb muscles in two decerebrate cats 36 mo after unilateral section and immediate surgical repair of the common nerve supplying the lateral gastrocnemius (LG) and soleus (S) muscles. 2. The production of considerable reflex force by reinnervated muscles in response to electrical stimulation of uninjured nerves indicated substantial functional recovery of motor units. However, reduction in the responsiveness of reinnervated muscles to stretch of the untreated medial gastrocnemius (MG) muscle indicated some deficit in recovery of normal synaptic integration. 3. Stretch failed to elicit autogenic excitation of the reinnervated S and LG. This failure was observed whether the reinnervated muscles were quiescent or contracting in other reflexes. 4. The heterogenic reflex organization of reinnervated muscles was abnormal. Stretch of the reinnervated S failed to evoke heterogenic reflexes both in the untreated MG and in the reinnervated LG. Stretch of the reinnervated LG failed to produce excitation of MG. 5. These findings demonstrate deficiencies in proprioceptive feedback from reinnervated muscles and lead us to expect incomplete recovery of motor function after nerve section

Cossu G., Valls-Sole J., Valldeoriola F., Munoz E., Benitez P., and Aguilar F. (1999) Reflex excitability of facial motoneurons at onset of muscle reinnervation after facial nerve palsy. Muscle Nerve 22, 614-620.
Abstract: We studied 18 patients with complete unilateral denervation of the facial muscles after idiopathic facial nerve palsy to determine whether motoneuronal excitability is enhanced in the few motor units that are active at onset of muscle reinnervation. The study was carried out between 75 and 90 days after the facial nerve lesion. We used two needle electrodes to record simultaneously the spontaneous and voluntary activity of the orbicularis oris (OOris) and orbicularis oculi (OOculi) muscles, as well as the responses to ipsilateral and contralateral facial and supraorbital nerve stimuli. All patients showed involuntary firing of motor unit action potentials (MUAPs) in at least one of the muscles. Synkinetic activation of motor units in the OOris was induced by spontaneous blinking in all patients, and by inhalation and swallowing in some. Electrical stimulation of the ipsilateral facial nerve induced a direct M response in only 4 patients. In contrast, long-latency reflex responses were induced in both muscles by electrical stimulation of ipsilateral and contralateral facial and supraorbital nerves in all patients, at latencies ranging between 44 and 132 ms. The shape of such MUAP reflex responses was the same as that of the MUAPs seen to fire at rest. These findings provide evidence of enhanced excitability of facial motoneurons in our patients. Such hyperexcitability may be partly responsible for the postparalytic motor dysfunction syndrome that occurs after facial palsy with severe axonal damage

Daniel R.K., Egerszegi E.P., Samulack D.D., Skanes S.E., Dykes R.W., and Rennie W.R. (1986) Tissue transplants in primates for upper extremity reconstruction: a preliminary report. J. Hand Surg. [Am.] 11, 1-8.
Abstract: Recent advances in clinical transplantation surgery suggest that hand transplantation is no longer an unrealistic expectation. However, two questions must be answered. Can composite tissue transplants survive in a primate species? Does the required neural reinnervation occur under immunosuppression? Four hand transplants and seven neurovascular free flap transplants were done in baboons immunosuppressed with Cyclosporin A and steroids (methylprednisolone). Long-term survival occurred in nine. Electrophysiologic tests of sensory axons revealed reinnervation of transplanted skin as evidenced by well-defined, low threshold receptive fields in the donor tissue. Reinnervation of donor muscle was demonstrated by motor unit recruitment in stepwise fashion after electrical stimulation of the recipient's median and ulnar nerves. Afferent fibers serving the donor's joints and muscle spindles were also observed

de Bisschop G. (1983) [Strategy for the prevention and treatment of post-paralytic facial syncinesis]. Ann. Otolaryngol. Chir Cervicofac. 100, 581-586.
Abstract: The existence of facial heimspasm and post-paralytic syncinesia is in general interpreted as the result of aberrant reinnervation following a Bell's palsy. In a certain number of cases, electrophysiological tests reveal synaptic abnormalities in the facial nucleus. These findings must be taken into consideration, together with the possibility of ephapsic stimulation of the proximal part of the facial nerve, when explaining the regression of syncinesia which is found in certain patients during the reinnervation phase. Prevension is based principally upon the quality of treatment and the rapidity with which both electrophysiological testing is undertaken and treatment started. It is important to avoid treatment aimed at accelerating reinnervation (neuronotrophic factors, dielectrolysis, etc . . . The process should take

place naturally. Electrical stimulation, administered under conditions of choice of current on the basis of the lesion, experimentally prevents dissemination of reinnervation. Repeated evaluation of possible diffusion of the blink reflex can be used to detect sub-clinical stages of progression to syncinesia. It would seem necessary to review from a particular standpoint the organised programming of physiotherapy and its association with biofeedback-EMG techniques. If signs of syncinesia develop, appropriate physiotherapy, biofeedback-EMG techniques and contralateral strio-motor electrotherapy combined with sedative and anti-paroxysmal therapy should be started

Eberstein A. and Pachter B.R. (1986) The effect of electrical stimulation on reinnervation of rat muscle: contractile properties and endplate morphometry. Brain Res. 384, 304-310.
Abstract: Denervated extensor digitorum longus muscles of Wistar rats were electrically stimulated in vivo for 4 days (2h per day) after peroneal nerve crush 1 cm from the muscle. Isometric contractile properties and endplate ultrastructure were measured on days 11 and 18. On day 11, the time to peak (116% of control) and 1/2-relaxation time (136% of control) for the twitch tensions of stimulated muscles measured in vivo were significantly less than those (127% and 157% of controls, respectively) of non-stimulated muscles. Peak twitch and tetanic tensions were not significantly different. The postsynaptic area of endplates for stimulated muscles were closer in size to controls than those for the non-stimulated ones. On day 18, no difference was found in the contractile responses between stimulated and non-stimulated groups. Similarly, the postsynaptic areas were the same for both groups. These results demonstrate that denervated muscle stimulated electrically for 4 days prior to reinnervation can preserve the structure of the endplate as well as accelerate recovery of normal function in reinnervated muscle fibers after 11 days of denervation

Erb D.E., Mora R.J., and Bunge R.P. (1993) Reinnervation of adult rat gastrocnemius muscle by embryonic motoneurons transplanted into the axotomized tibial nerve. Exp. Neurol. 124, 372-376.
Abstract: In some cases of spinal cord injury and in certain motoneuron diseases, such as amyotrophic lateral sclerosis and spinal muscular atrophies, lower motoneurons are destroyed and muscle function cannot be restored except by reinnervation from alternate motoneuron sources. We have tested the feasibility of employing local transplantation of embryonic motoneurons to restore innervation to denervated somatic muscle as a first step in salvaging muscle function and enabling use of functional electric stimulation. Dissociated ventral spinal cord cells from Embryonic Days 14 and 15 rats were transplanted into the distal stump of axotomized tibial nerves of adult rats. Animals were killed 3-18 weeks after transplantation. After 3 weeks large multipolar cells, resembling alpha motoneurons, were observed within the transplant site surrounded by myelinated and unmyelinated axons and dendrites. Axons emanating from these transplanted motoneurons were identified within the nerve stump and within the previously denervated gastrocnemius muscle, forming neuromuscular junctions. Transplanted motoneurons survived up to 18 weeks and were labeled after intramuscular injection of fast blue. This study demonstrates that embryonic spinal motoneurons, transplanted into the distal adult peripheral nerve stump, are able to survive and reinnervate the denervated target muscle. We are now exploring the possibility of using this experimental approach to

retard the atrophy of denervated skeletal muscle, thus providing a muscle capable of useful response to functional electrical stimulation

Gaillard S. and Horvat J.C. (1993) [Model of "bridge" graft between the cervical spinal cord and biceps muscle using a peripheral nerve autograft. Study in adult rats]. Chirurgie 119, 649-656.
Abstract: The authors present, in the adult rat, a model of reconnection between an injured cervical spinal cord (C5) and the biceps brachii muscle (BB) previously denervated, by means of an autologous peripheral nerve segment (PNG). The study includes 30 rats shared into 4 principal groups: A) the denervation of BB by transection and ligature of the musculocutaneous nerve (MCN); B) transection and immediate suture of the MCN; C) transection/ligature of the MCN and insertion of a PNG both into the cervical spinal cord and into the BB; D) transection of the MCN, ligature of its proximal tip, insertion of one end of a PNG into the cervical spinal cord and suture of the other end with the distal stump of the MCN. Assessment of the following parameters were performed, in all animals, three months after the grafting procedure: 1) the muscle strength by using the toilet test; 2) the weight of the experimental BB in comparison to the contralateral BB; 3) the response (contraction) of the BB under electrical stimulation of either the MCN or the PNG; 4) the histological appearance of the BB; 5) the presence of retrogradely labelled neuronal somata in the cervical spinal cord following application of horseradish peroxidase (HRP) to the MCN or to the GNP. These parameters of evaluation have at first been validated in two cases already known: the chronic denervation of the BB (group A), and the peripheral nerve lesion (group B). Once these cases validated, they have been used to appreciate the muscular reinnervation by axonal growth from the spinal cord.(ABSTRACT TRUNCATED AT 250 WORDS)

Gordon T. and Mao J. (1994) Muscle atrophy and procedures for training after spinal cord injury. Phys. Ther. 74, 50-60.
Abstract: Functional electrical stimulation (FES) of paralyzed muscles holds promise as a strategy to assist patients in executing functional movements after spinal cord injuries. Muscle atrophy is one of the major problems that must be addressed for this approach to be successful. Loss of muscle mass may occur as a result of lesions to motoneurons in either the spinal cord or the central command pathway, or a combination of the two. For injuries to spinal motoneurons, muscle fibers undergo denervation atrophy. Damage to the central command pathway, on the other hand, results in disuse atrophy. In association with atrophy, the low contractile forces and inability of the muscles to sustain contractions are of direct therapeutic concern. In this review, methods aimed at recovery of function of paralyzed limbs by reducing susceptibility to fatigue and atrophy of paralyzed muscles are discussed. One is related to promoting nerve sprouting in partially denervated muscles to reinnervate muscle fibers and reverse denervation atrophy. The other regards training of paralyzed muscles to increase strength (muscle force) and endurance (fatigue resistance) by means of FES. Most training regimens with low-frequency FES increase muscle endurance. Efforts to design optimal regimens for increasing both muscle strength and endurance must involve consideration of several factors that are still controversial. These factors, which include muscle properties (such as fiber type composition and physiological type) and conditions imposed on the muscle (such as loading) during contractions elicited by FES, are discussed in detail

Gordon T. (1995) Fatigue in adapted systems. Overuse and underuse paradigms. Adv. Exp. Med. Biol. 384, 429-456.
Abstract: Alterations in structural and biochemical properties of muscles that underlie physiological parameters of contractile force, speed and fatigability are described under conditions of 1) overuse: imposed electrical stimulation, natural exercise and functional overload; 2) reinnervation of denervated muscles; and 3) underusage: conditions of restricted use after spinal cord injury, weightlessness, immobilization and drug-induced neuromuscular blockade. These conditions demonstrate the remarkable plasticity of muscle fibers with obvious implications in health and disease. They also identify that the amount of neuromuscular activity and loading of muscle contractions are major factors determining susceptibility to fatigue and muscle strength, respectively

Green D.C., Berke G.S., and Graves M.C. (1991) A functional evaluation of ansa cervicalis nerve transfer for unilateral vocal cord paralysis: future directions for laryngeal reinnervation. Otolaryngol. Head Neck Surg. 104, 453-466.
Abstract: There are a variety of methods for treating unilateral vocal cord paralysis, but to date there are few objective studies that evaluate the functional results of nerve transfer from the ansa cervicalis. Six dogs underwent unilateral recurrent laryngeal nerve section with immediate reanastamosis to the sternothyroid branch of the ansa cervicalis. After 5 to 6 months, measurements of vocal efficiency and acoustic parameters, videolaryngoscopy, videostroboscopy, and evoked electromyography were performed. Identical measurements were made in eight control dogs during normal electrically induced phonation and a simulated unilateral recurrent laryngeal nerve paralysis. Histologic analysis of both vocalis muscles, recurrent laryngeal nerves, ansa cervicalis, and the ansa-recurrent laryngeal nerve anastamosis site was performed. Evidence of reinnervation was found in all of the animals that underwent nerve transfer. The vocal efficiency and acoustic quality after ansa cervicalis nerve transfer were dependent on the degree of electrical stimulation from the transferred nerve to the reinnervated cord during phonation. In the absence of electrical stimulation to the nerve transfer, physiologic vocal cord motion could not be elicited from the reinnervated cord

Gurney M.E. (1984) Suppression of sprouting at the neuromuscular junction by immune sera. Nature 307, 546-548.
Abstract: Injury of afferent motor axons or pathological loss of motoneurones from the spinal cord causes the remaining axons within a muscle to sprout and to reinnervate the denervated muscle fibres. Sprouting occurs at two sites along intramuscular axons, at nodes of Ranvier (nodal sprouting) and at the neuromuscular junction (terminal sprouting). Terminal sprouting is also produced by treatment with botulinum toxin and by other agents that render muscle inactive. The muscle probably provides a signal for terminal sprouting as restoration of muscle activity by direct electrical stimulation prevents sprouting. Such a signal might be a local change on the muscle fibre surface or a 'soluble' sprouting factor, although the failure to induce terminal sprouting in one muscle by denervating adjacent muscles argues against the latter hypothesis. I now report that rabbit antisera against a 56,000 (56K)-molecular weight protein secreted by denervated rat muscle suppress botulinum toxin-induced terminal sprouting in the mouse gluteus muscle. An immune response against this protein has also been detected in serum of patients with amyotrophic lateral sclerosis (ALS), a disease in which loss of motoneurones from the spinal cord

is not accompanied by the degree of sprouting and reinnervation seen in other motoneurone diseases

Herbison G.J., Teng C.S., and Gordon E.E. (1973) Electrical stimulation of reinnervating rat muscle. Arch. Phys. Med. Rehabil. 54, 156-160.

Herbison G.J., Jaweed M.M., Ditunno J.F., Scott C.M. (1974) Overwork of Denervated Skeletal Muscle. *Arch Phys Med Rehabil* 55, 202-205.

Herbison G.J., Jaweed M.M., Ditunno J.F. (1974) Effect of swimming on reinnervation of rat skeletal muscle. *J Neurol, Neurosurg & Psychiat* 37, 1247-1251.

Herbison G.J., Jaweed M.M., Ditunno J.F. (1980) Effect of activity on reinnervating rat skeletal muscle contractility. *Exp Neurol* 70, 498-506.

Herbison G.J., Jaweed M.M., Ditunno J.F. (1980) Histochemical Fiber Type Alterations Secondary to Exercise Training of Reinnervating Adult Rat Muscle. *Arch Phys Med Rehabil* 61, 255-257.

Herbison G.J., Jaweed M.M., Ditunno J.F. (1981) Contractile Properties of Reinnervating Skeletal Muscle in the Rat. *Arch Phys Med Rehabil* 62, 35-39.

Herbison G.J., Jaweed M.M., Ditunno J.F. (1982) Reinnervating Rat Skeletal Muscle: Effect of 35% Grade Treadmill Exercise. *Arch Phys Med Rehabil* 63, 313-316.

Herbison G.J., Jaweed M.M., and Ditunno J.F., Jr. (1983) Exercise therapies in peripheral neuropathies. Arch. Phys. Med. Rehabil. 64, 201-205.
Abstract: The treatment of peripheral neuropathies should be aimed at maintaining the range of motion of the joints, re-educating the patient in skilled activities and optimizing the recovery of strength. Many techniques have been described to substitute for, to strengthen and to improve the function of residual innervated muscle; however, not all of these techniques are of unquestioned value. Specifically, electrical stimulation does not appear to enhance reinnervation of totally denervated muscle. Similarly, overstretching weakened muscle may impair the use of paretic muscle. Because overwork may damage partially denervated muscle, brief isometric or isotonic contractions may be more beneficial for increasing strength than a program of habitual exhausting activities

Herbison G.J., Jaweed M.M., and Ditunno J.F., Jr. (1983) Acetylcholine sensitivity and fibrillation potentials in electrically stimulated crush-denervated rat skeletal muscle. Arch. Phys. Med. Rehabil. 64, 217-220.
Abstract: Juxtamuscular electrodes were implanted unilaterally in six groups of adult female Wistar rats to evaluate the effect of chronic electrical stimulation (ES) during denervation and reinnervation of the rat soleus muscle. Two weeks later, the animals underwent bilateral crush- denervation of the sciatic nerve at the sciatic notch. Six additional groups served as normal controls. The soleus muscles in the crush denervated and control groups were stimulated unilaterally with a 4mA, 4msec duration current given at 10Hz continuously 8 hours each day for 5, 10, 15, 20, 25 or 30 days. At the end of each period, the soleus muscles were evaluated for the muscle weights, acetylcholine (ACh) sensitivity and fibrillation potentials (FPs). The normal muscles were unaffected by the stimulation. The denervated-stimulated

soleus muscles were heavier at 10 days (p less than 0.05) and had fewer FPs after 5 to 15 days (p less than 0.01) of electrical stimulation than their matched denervated controls. The ACh sensitivity throughout the experimental period and the fibrillatory activity from 20 to 30 days post-crush were similar in the denervated and the denervated-stimulated muscles. In conclusion, ES reduced the degree of atrophy and the number of fibrillations of the soleus muscle in the denervation stage. However, it neither enhanced nor impaired the reinnervation of muscle

Herbison G.J., Jaweed M.M., Ditunno J.F. (1986) Electrical Stimulation of Sciatic Nerve of Rats After Partial Denervation of Soleus Muscle. *Arch Phys Med Rehabil* 67, 79-83.

Herrmann V. and Bergmann K. (1987) [Long-term experimental electric stimulation of denervated laryngeal muscles in dogs. Myopathologic findings]. Zentralbl. Allg. Pathol. 133, 337-350.
Abstract: The recurrent laryngeal nerve was transsected unilaterally and a device for electrical stimulation of the denervated muscles was implanted in 6 dogs. After 3 to 11 months the laryngeal muscles were obtained and histopathologically demonstrated a striking neurogenic pattern. In place of homogeneous muscle fiber atrophy, a patchwork of grouped fibre atrophy, compensational hypertrophy, fibre regeneration and reinnervation as well as muscle fibre type grouping were observed. Muscle fibre type distribution in the m. cricoarytenoideus posterior, m. vocalis and m. cricothyroideus was determined and compared between the normal and denervated sites. All muscles showed some changes in the fibre type distribution, including type grouping, but these were most pronounced in m. vocalis. The average fibre diameter decreased whereas fibre size variability increased. Mixed muscle fibre atrophy with compensatory hypertrophy of a single fibre type predominated. There was no evidence of disuse atrophy. The electrically stimulated muscles could be maintained at a reduced functional level throughout the study period

Jaweed M.M., Herbison G.J., and Ditunno J.F. (1982) Direct electrical stimulation of rat soleus during denervation- reinnervation. *Exp. Neurol*. 75, 589-599.

Kinney C.L., Jaweed M.M., Herbison G.J., Ditunno J.F. (1986) Overwork effect on partially denervated rat soleus muscle. *Arch Phys Med Rehabil* 67:286-289.

Koerber H.R. and Mirnics K. (1996) Plasticity of dorsal horn cell receptive fields after peripheral nerve regeneration. J. Neurophysiol. 75, 2255-2267.
Abstract: 1. The tibial and sural nerves were transected and repaired in nine adult cats. The receptive field (RF) properties of dorsal horn neurons were examined at three different intervals (5-6, 9, or 12 mo) after axotomy. The properties examined included RF location, area, and modality convergence. In some cases, discrete areas of the cell's RF were stimulated electrically while the evoked cord dorsum potentials (CDPs) and any intracellularly recorded responses were simultaneously recorded. 2. At the shortest interval following reinnervation, the somatotopic organization in the affected areas of the dorsal horn was lost. Dorsal horn cells that received input primarily from regenerated fibers had large, low-threshold excitatory RFs that contained much of the reinnervated skin. Those cells with RFs restricted to a fraction of the reinnervated skin had significant components of their RFs on the foot dorsum supplied by intact fibers (i.e., superficial peroneal nerve). 3. At longer intervals the somatotopic organization remained scrambled. Dorsal horn cell low-

threshold RFs were significantly reduced in size. Many cells exhibited large areas of excitatory subliminal fringe and concise inhibitory RFs. In addition, those cells that responded to peripheral stimuli across a wide range of stimulus intensities (wide-dynamic-range cells) also exhibited plasticity in the relative sizes of their low- and high-threshold RFs. 4. At the shortest recovery time, focal electrical stimulation of the skin within the RF of an impaled cell and simultaneous recordings of the evoked CDPs and postsynaptic potentials revealed that at numerous locations within the initial large RFs, single fibers or small groups of fibers could be electrically activated that were not connected to the dorsal horn cell. At the longer recovery times there was a much higher incidence of connectivity. 5. These results suggest that mechanisms affecting both synaptic efficacy of afferent fiber connections and/or the establishment of afferent-driven inhibitory inputs may effect the reshaping of dorsal horn cell RFs after reinnervation. These results are discussed in relation to their potential contribution to previously observed cortical plasticity and functional recovery following similar lesions

Koller R., Happak W., Frey M., Neumayer C., Girsch W., Liegl C., and Gruber H. (1997) [Comparative studies of morphometric and functional results following reconstruction of motor nerves]. Handchir. Mikrochir. Plast. Chir 29, 330-334.
Abstract: In order to determine the value of a reconstructive procedure in the peripheral nerve, experimental studies often evaluate the number and the diameter of myelinated nerve fibers as a parameter for the quality of regeneration. This study addresses the correlation between the number of fibers in a peripheral motor nerve after microsurgical reconstruction and the functional result, expressed as the force of the reinnervated muscle. In a total number of 24 sheep, the motor branch to the rectus femoris muscle was severed. The muscle was reinnervated either by direct neurorrhaphy or by nerve grafting, performed in three different ways (free grafting to the ipsilateral muscle, free grafting to the contralateral muscle, vascularized grafting to the ipsilateral muscle). In the final experiments, the muscle force in the reinnervated muscle was determined by supramaximal electrical stimulation. Number and diameter of myelinated nerve fibers were evaluated by computer- assisted morphometric analysis. Regression analysis of morphometric data and the muscle forces was calculated. No correlation was found between fiber numbers in the nerve graft and the maximal force. However, a positive correlation between the number of myelinated fibers in the motor branch distal to the site of coaptation and the functional result was observed in some cases. The diameter of myelinated fibers had no influence on the functional outcome

Lewis D.M., al Amood W.S., and Schmalbruch H. (1997) Effects of long-term phasic electrical stimulation on denervated soleus muscle: guinea-pig contrasted with rat. J. Muscle Res. Cell Motil. 18, 573-586.
Abstract: Guinea-pig soleus muscles were denervated and electrically stimulated for periods of 43 to 66 days. Stimuli were in 1 s bursts of 40 Hz pulses, repeated every 5 min. Other guinea-pigs were denervated for 82 days without stimulation and, in a third group, the soleus muscle was necrotized and allowed to regenerate without reinnervation for 13-15 days. Isometric and isotonic recordings were made in vivo. Denervated guinea-pig muscles were embedded in epoxy resin for light and electron microscopy. Chronic stimulation of denervated guinea-pig soleus had no effects on the prolonged twitch or on reduced maximal shortening velocity, maximal rate of rise of tension and tetanic force. This contrasts with the slow-to-fast conversion produced by denervation and denervation-stimulation of rat soleus. Loss of force was much

greater in rat than guinea-pig after denervation, and chronic stimulation increased force in rat to the same level as in guinea-pig after denervation (with or without stimulation). Eighty-day denervated guinea- pig soleus did not reveal those morphological signs of fibre breakdown and regeneration which are prominent in denervated rat soleus muscles. Those changes in rat resembled aneurally regenerated muscles in several aspects, especially the increased incidence of fibres with internal myo- nuclei which did not appear in guinea-pig soleus after denervation. Aneurally regenerated guinea-pig soleus became fast like aneurally regenerated rat muscle. Our data are compatible with the hypothesis that slow-to-fast transformation of denervated rat soleus is not directly brought about by chronic stimulation but by de-novo formation of fast-contracting regenerated fibres. The persistence of fibrillation in guinea-pig but not rat after denervation may account for the species difference

Lieber R. (2002) *Skeletal Muscle Structure, Function and Plasticity: the Physiological Basis of Rehabilitation, Ed 2.* Philadelphia, Lippincott, Williams & Wilkins, pp 271-274.

Matsushita H. (1989) [Changes in concentrations of nerve- and muscle-related proteins during reinnervation of slow and fast muscles]. Aichi. Gakuin. Daigaku Shigakkai. Shi 27, 397-413.
Abstract: The concentration of the nerve-related (gamma-enolase) and muscle-related (beta-enolase and creatine kinase of B type) proteins was measured in the rat sciatic nerve and the muscles; soleus (SOL), a typical slow-twitch muscle, and extensor digitorum longus (EDL), a typical fast-twitch muscle. The nerves and muscles were subjected to experimental manipulation of their innervation. 1. Nerve-related protein, gamma-enolase. The concentration of gamma-enolase in the distal part of the transected sciatic nerve was decreased in 2 weeks to about 10% of normal. When the sciatic nerve was sutured immediately after the transection, the concentration of gamma-enolase recovered in 34 weeks to a level of about 62.8% of normal. 2. Fast muscle-related protein, beta-enolase. The concentration of the beta-enolase in the SOL and the EDL was reduced after sciatic nerve transection. When the sciatic nerve was sutured immediately after complete transection, the concentration of beta-enolase of SOL and EDL became almost equal on the 34th week. After cross union of the nerves innervating the SOL and EDL muscles, the concentration of the beta-enolase were almost equal on the 20th post-operative week in the both muscles, and reversed on the 34th week. The beta-enolase concentrations in the SOL and EDL muscles innervated by the TTX-perfused sciatic nerve were reduced to 72.3% and 70.4%, respectively. Continuous electrical stimulation of the sciatic nerve reduced the beta-enolase concentration in the EDL to 51.8% of normal, but did not affect the SOL significantly. 3. Slow muscle- related protein, creatine kinase of B type (CK-B). After complete severance of the sciatic nerve the CK-B concentration showed a marked increase in the both muscles. When the sciatic nerve was sutured immediately after transection, the CK-B concentration on the 34th week was about 35.3% in the SOL and close to normal in the EDL. On the 34th week after cross union of the nerves innervating the SOL and EDL muscles, the CK-B concentration was reduced to about 41.1% in the SOL, while it was increased to about 111% in the EDL. On the 20th week after self re-union of the nerves innervating the SOL and EDL muscles, the CK- B concentration in the EDL recovered the normal level, but in the SOL muscle it was increased significantly. 4. It appears that the measurement of the concentration of gamma-enolase, beta-enolase

and CK- B can provide valuable informations on the recovery course of skeletal muscles after nerve injury

McCallister W.V., Tang P., and Trumble T.E. (1999) Is end-to-side neurorrhaphy effective? A study of axonal sprouting stimulated from intact nerves. J. Reconstr. Microsurg. 15, 597-603.
Abstract: The purpose of this study was to determine if axonal sprouting across an end-to-side coaptation could be stimulated and if so, to identify the source of the regenerating axons. Mechanical trauma, the method used to stimulate axonal sprouting, was compared to a control group with coaptation only and an additional non-grafted control group. After a 20-week recovery period, electrical stimulation revealed that the target muscles had been reinnervated in all groups except the non-grafted control group. Axonal counting demonstrated a significant increase for the mechanical trauma group compared to the control group with coaptation only [ratio of the density of axons/microm2 of the experimental to the contralateral control side: 2.78+/-0.11 vs. 0.96+/- 0.15, respectively, p<0.002). Tibialis anterior muscle weights were significantly increased for both groups vs. the non-grafted control group (ratio of experimental to the contralateral control side: coaptation-only control, 0.539+/-0.024; mechanical trauma, 0.538+/- 0.036 vs. nongrafted control, 0.220+/-0.003, p<0.002). Of importance, this study provides evidence that the intact tibial nerve functions as a bridge for regenerating axons derived from the proximal peroneal stump. This suggests an alternative explanation to successful end-to- side axonal sprouting, and questions the clinical utility of end-to- side coaptation

McDevitt L., Fortner P., and Pomeranz B. (1987) Application of weak electric field to the hindpaw enhances sciatic motor nerve regeneration in the adult rat. Brain Res. 416, 308-314.
Abstract: Direct current (DC) electrical stimulation of the hindpaw is shown to enhance sciatic motor nerve regeneration in the adult rat. Cathodal stimulation, using weak currents (10 microA/cm2; field strength approximately 100 mV/cm) increased the reinnervation of the hindpaw muscles as measured by evoked electromyograms. This enhanced regeneration only occurred after cut-and-suture lesions, but not after crushing injury of the sciatic nerve. This enhancement of motor nerve regeneration by weak DC fields had been previously described in amphibians but we are the first to describe this phenomenon in mammals

Montserrat L. and Benito M. (1990) Motor reflex responses elicited by cutaneous stimulation in the regenerating nerve of man: axon reflex or ephaptic response? Muscle Nerve 13, 501-507.
Abstract: In 57 of 60 nerves (29 median and 31 ulnar) sutured at the wrist, forearm and arm, we recorded motor responses in thenar or hypothenar muscles by electrical stimulation of the corresponding fingers. Recordings were made at different times during the process of regeneration, ranging from 3 months up to 11 years. The responses showed a constant shape and latency to every stimulation (simple or repetitive). The latency was shorter the more distal the level of injury and the greater the elapsed time from the reinnervation. The point of "reflexion" of the responses is at or very near the line of nerve suture. The electrophysiological behavior of the responses fits well with either the criterion of axon reflex or ephaptic response. We discuss both possibilities and conclude that it is not possible, with the electrophysiological technique that we used, to distinguish between an axon reflex and an ephaptic response

Nakatsuchi Y., Matsui T., and Handa Y. (1980) Funicular orientation by electrical stimulation and internal neurolysis in peripheral nerve suture. Hand 12, 65-74.
Abstract: Eleven peripheral nerve lacerations around the wrists of ten patients were treated with funicular suture or nerve graft. In three freshly lacerated nerves funicular orientation could be made only by electrical stimulation to both cut ends. The electrophysiological method was also utilised to obtain funicular orientation of a proximal stump in eight old nerve lacerations. However, funicular orientation of the distal stump of old lacerations, which was not responsive to electrical stimulation, was performed anatomically by internal neurolysis from a terminal branching area up to a distal stump. By six months after the operation, motor and sensory functions of the patients with funicular suture had recovered to an excellent degree with rapid reinnervation

Navarro X. and Kennedy W.R. (1990) Changes in sudomotor nerve territories with aging in the mouse. J. Auton. Nerv. Syst. 31, 101-107.
Abstract: This study evaluates sudomotor function in the hindpaw of young and aged mice. Sweating was stimulated by pilocarpine injection and by electrical stimulation of the sciatic, tibial, peroneal, sural and saphenous nerves. The number of responsive sweat glands of the paw was determined by the silicon mold technique. The results obtained provide evidence that the number of functioning sweat glands of the hindpaw tended to decrease in aged mice. The peripheral sudomotor territories and the complement of sweat glands for individual nerves declined slightly with age. Moreover, the number of sweat glands responsive to cholinergic stimulation was decreased when compared with the number responsive to electrical stimulation of the sciatic nerve in aged mice. These and previous observations suggest that the number of sudomotor axons in the peripheral nerve, as well as their capabilities for compensatory reinnervation of sweat glands by regeneration and by sprouting, is reduced with aging

Ochi M., Iwasa J., Uchio Y., Adachi N., and Sumen Y. (1999) The regeneration of sensory neurones in the reconstruction of the anterior cruciate ligament. J. Bone Joint Surg. Br. 81, 902-906.
Abstract: We examined whether somatosensory evoked potentials (SEPs) were detectable after direct electrical stimulation of injured, reconstructed and normal anterior cruciate ligaments (ACL) during arthroscopy under general anaesthesia. We investigated the position sense of the knee before and after reconstruction and the correlation between the SEP and instability. We found detectable SEPs in all ligaments which had been reconstructed with autogenous semitendinosus and gracilis tendons over the past 18 months as well as in all cases of the normal group. The SEP was detectable in only 15 out of 32 cases in the injured group, although the voltages in the injured group were significantly lower than those of the controls. This was not the case in the reconstructed group. The postoperative position sense in 17 knees improved significantly, but there was no correlation between it and the voltage. The voltage of stable knees was significantly higher than that of the unstable joints. Our findings showed that sensory reinnervation occurred in the reconstructed human ACL and was closely related to the function of the knee

Pachter B.R., Eberstein A. (1989) Passive Exercise and Reinnervation of the Rat Denervated Extensor Digitorum Longus Muscle after Nerve Crush. *Am J Phys Med Rehabil* 68:179-182.

Panenic R. and Gardiner P.F. (1998) The case for adaptability of the neuromuscular junction to endurance exercise training. Can. J. Appl. Physiol 23, 339-360.
Abstract: Although the adaptability of the neuromuscular junction (NMJ) has been demonstrated using the models of denervation/reinnervation, electrical stimulation, development, aging, and pathological states, relatively little is known about the effects of increased chronic voluntary use on the morphology and physiological function of the NMJ. A review of findings relating to adaptations in the various pre- and postsynaptic components of the NMJ with exercise training is presented. These findings are discussed as they pertain to NMJ function during exercise. Other physiological modulators of the NMJ, such as trophic factors released by nerve terminals and muscles, and circulating substances are discussed in terms of possible roles they may play in training-induced adaptations

Reiness C.G., Hogan P.G., Marshall J.M., and Hall Z.W. (1977) Factors influencing degradation of extrajunctional acetylcholine receptors in skeletal muscle. Prog. Clin. Biol. Res. 15, 207-215.
Abstract: During development and after both denervation and reinnervation in adult mammalian skeletal muscle, the level of acetylcholine (ACh) receptors in the extrajunctional membrane undergoes wide variation. We have determined the rate of extrajunctional receptor degradation in denervated muscles in organ culture under a variety of conditions by measuring the rate at which alpha-bungarotoxin bound to the receptors is degraded. Direct electrical stimulation of muscles for several days dramatically reduced the levels of extrajunctional ACh sensitivity, and also reduced the rate of receptor degradation. Since the effect of activity on the rate of receptor degradation is in the opposite direction of the observed change in receptor levels, we conclude that activity must also decrease the rate of receptor synthesis. Receptor degradation was also examined in muscles at various times after denervation. The half-time of degradation increased from approximately 7 hr at 2-5 days after denervation to approximately 14 hr at 10-14 days. Hypophysectomy, which decreases the average rate of protein degradation in muscle, also decreased the rate of extrajunctional receptor degradation, but thyroxine, which restores the normal rate of overall protein breakdown in hypophysectomized animals, did not affect receptor breakdown. Since hypophysectomy did not increase the level of extrajunctional ACh receptors, it must also affect ACh receptor synthesis

Salmons S. and Sreter F.A. (1976) Significance of impulse activity in the transformation of skeletal muscle type. Nature 263, 30-34.
Abstract: The changes which follow cross reinnervation of mammalian fast and slow twitch muscles may reflect a capacity of skeletal muscle to respond adaptively to different functional requirements. This interpretation is supported by experiments in which long-term electrical stimulation was used both to reproduce and to oppose the effects of cross reinnervation

Sanes J.R., Covault J. (1985) Axon guidance during reinnervation of skeletal muscle. *Trends in Neurosciences* 8:523-528.

Sanes J.R., Lichtman J.W. (1999) Development of the vertebrate neuromuscular junction. *Annual Review of Neuroscience* 22:389-442.

Schimrigk K., McLaughlin J., and Gruninger W. (1977) The effect of electrical stimulation on the experimentally denervated rat muscle. Scand. J. Rehabil. Med. 9, 55-60.

Abstract: The m. quadriceps of white rats was electrically stimulated after nerve crush and after nerve section. Electrically stimulated muscles showed fewer central nuclei and a greater number of necrotic single fibres. The demonstration of motor endplates could not give a reliable indication of the onset of reinnervation. The various results show the importance of the trophic influence of the nerve and raise the suspicion that electrical stimulation has a retarding effect on the atrophy but also on regeneration of the fibres. After 7 weeks the unstimulated muscles show a greater degree of regeneration than the stimulated ones

Smith K.J. and Kodama R.T. (1991) Reinnervation of denervated skeletal muscle by central neurons regenerating via ventral roots implanted into the spinal cord. Brain Res. 551, 221-229.
Abstract: The reinnervation of denervated skeletal muscle by central axons regenerating via a ventral root implanted into the spinal cord was examined in rats. The 8th thoracic ventral root was severed and its distal end implanted into the ventro-lateral column of the spinal cord via a stab incision. In control animals the root was severed, but was not implanted into the stab incision. After 12-14 months the animals were examined electrophysiologically to determine the presence or absence of motor units in the 8th intercostal muscle which were reinnervated by centrally derived axons regenerating via the implant. Such units were found in implanted animals, but in none of the controls. Evidence that the motor units were reinnervated by central axons included the facts that the units could be activated either, (1) reflexly (i.e. trans-synaptically) by electrical stimulation of the dorsal roots or spinal cord, or (2) pharmacologically by either the intraspinal injection of glutamate or acetycholine, or by the systemic administration of strychnine. Great care was taken to ensure that the only feasible connection between the spinal cord and the 8th intercostal muscle was via the site of implantation. The EMG signals from the motor units were of large amplitude, typical of reinnervated muscle, and their individual activation resulted in discernible contractions of regions of the T8 intercostal muscle. We conclude that regenerating CNS neurons can be guided to innervate denervated skeletal muscle by the implantation of severed ventral roots into the spinal cord. The neuromuscular synapses formed are functional and persistent. The findings may be relevant to the restoration of function after nervous injuries, such as the avulsion of ventral roots

Soucy M., Seburn K., Gardiner P. (1996) Is increased voluntary motor activity beneficial or detrimental during the period of motor nerve regeneration/reinnervation? *Can J Appl Physiol* 21:218-224.
Abstract: A model of partial denervation of the rat lateral gastrocnemius was used to investigate the effects of daily activity (treadmill plus voluntary wheel exercise) on the regeneration/ reinnervation of motoneurons recovering from nerve crush. It appears that increased activity has no effect on axon regeneration rate, but may be detrimental to the reinnervation process.

Stanco A.M. and Werle M.J. (1998) Agrin and acetylcholine receptor distribution following electrical stimulation. Muscle Nerve 21, 407-409.
Abstract: Electrical stimulation is a therapeutic modality available for the preservation of muscle function following peripheral nerve injury. Agrin, a synaptic basal lamina protein, induces accumulation of acetylcholine receptors (AChRs) and other molecules at the neuromuscular junction. Electrical stimulation of denervated muscle does not alter agrin and AChR distribution at abandoned synaptic sites, supporting

the hypothesis that the existing aggregation of synaptic molecules, which may be necessary for successful reinnervation, is unaltered by electrical stimulation of denervated muscle

Tam S.L., Archibald V., Jassar B., Tyreman N., Gordon T. (2001) Increased neuromuscular activity reduces sprouting in partially denervated muscles. *J Neurosci* 21:654-667.

Targan R.S., Alon G., and Kay S.L. (2000) Effect of long-term electrical stimulation on motor recovery and improvement of clinical residuals in patients with unresolved facial nerve palsy. Otolaryngol. Head Neck Surg. 122, 246-252.
Abstract: PURPOSE: This study investigated the efficacy of a pulsatile electrical current to shorten neuromuscular conduction latencies and minimize clinical residuals in patients with chronic facial nerve damage caused by Bell's palsy or acoustic neuroma excision. SUBJECTS: The study group included 12 patients (mean age 50.4 +/- 12. 3 years) with idiopathic Bell's palsy and 5 patients (mean age 45.6 +/- 10.7 years) whose facial nerves were surgically sacrificed. The mean time since the onset of paresis/paralysis was 3.7 years (range 1-7 years) and 7.2 years (range 6-9 years) for the Bell's and neuroma excision groups, respectively.Method And Procedures: Motor nerve conduction latencies, House-Brackmann facial recovery scores, and a 12-item clinical assessment of residuals were obtained 3 months before the onset of treatment, at the beginning of treatment, and after 6 months of stimulation. Patients were treated at home for periods of up to 6 hours daily for 6 months with a battery-powered stimulator. Stimulation intensity was kept at a submotor level throughout the study. Surface electrodes were secured over the most affected muscles. Groups and time factors were used in the analyses of the 3 outcome measures. RESULTS: No statistical differences were found between the two diagnostic groups with respect to any of the 3 outcome measures. Mean motor nerve latencies decreased by 1.13 ms (analysis of variance test, significant P = 0.0001). House-Brackmann scores were also significantly lower (Wilcoxon signed rank test, P = 0.0003) after treatment. Collective scores on the 12 clinical impairment measures decreased 28.7 +/- 8.1 points after 6 months [analysis of variance test, significant P = 0.0005). Eight patients showed more than 40% improvement, 4 better than 30%, and 5 less than 10% improvement in residuals score. CONCLUSION: These data are consistent with the notion that long-term electrical stimulation may facilitate partial reinnervation in patients with chronic facial paresis/paralysis. Additionally, residual clinical impairments are likely to improve even if motor recovery is not evident

Williams H.B. (1996) The value of continuous electrical muscle stimulation using a completely implantable system in the preservation of muscle function following motor nerve injury and repair: an experimental study. Microsurgery 17, 589-596.
Abstract: Functional recovery following motor nerve injury and repair is directly related to the degree of muscle atrophy that takes place during the period of nerve regeneration. The extent of this muscle atrophy is related to a number of factors including the accuracy of nerve repair; the distance through which the nerve must regenerate; the age of the patient; and the type of nerve injury and other associated tendon and soft tissue and bony damage. Atrophy of muscle that is always associated with nerve injury is a combination of disuse and degeneration. Our hypothesis proposed the following question: "Would continuous electrical stimulation of the denervated muscle during the period of nerve regeneration maintain the

integrity of the muscle fibers and hence their potential functional capacity?" We have completed a series of animal studies (rabbit and canine models) in our laboratory using a completely implantable system to provide continuous muscle stimulation following nerve injury and microsurgical repair. In several different experiments, the nerves under study were cut and repaired at 4 and 12 cm from the muscles to study the effects of short- and long-term recovery. In all experiments, a beneficial effect was demonstrated with improved morphology and functional capacity of the reinnervated stimulated muscles when compared with nonstimulated controls. In addition, electrical stimulation using this implantable system could be applied for extended periods without evidence of discomfort in the experimental animals

Wolf S.R. (1998) [Idiopathic facial paralysis]. HNO 46, 786-798.
Abstract: Although acute idiopathic facial paresis is often labelled "Bell's palsy", historical studies show that Nicolaus Anton Friedreich (1761- 1836) from Wurzburg was the first physician to describe the typical symptoms of the disorder in 1797, approximately 24 years prior to the paper published by Sir Charles Bell. Diagnostics has now improved to the extent that acute idiopathic facial palsy can more frequently be assigned to etiologies caused by inflammatory disorders. Herpes simplex virus type I and Borrelia burgdorferi are particularly relevant. Underestimation of the degree of paresis is, particularly in children, a drawback of the clinical examination. "Incomplete eyelid closure" is not a reliable indicator of remaining nerve function. For this reason complete electromyography (EMG) is recommended in all cases of severe facial paresis. Since electroneurography does not reliably reflect the degree of denervation present, needle EMG is preferred. The therapy of the facial palsy of unclear etiology is still not well defined. Nevertheless, we recommend that a combined treatment should be used early, at least in patients with disfiguring pareses. Combinations may consist of cortisone, virostatic agents and hemorrheologic substances and possibly antibiotics. Surgical decompression of the facial nerve remains controversial, since positive surgical results lack statistical support. Individual instructions for facial exercises, massage and muscle relaxation can support rehabilitation and possibly reduce the production of pathological synkinesia. Electrical stimulation should not be used. There are a number of possibilities available to reduce the effects of misdirected reinnervation, especially the use of botulinum-A-toxin. However, intensive diagnosis and therapy in the early phase of paresis are decisive in obtaining a favorable outcome. Further refinements in rehabilitation and comparative multicenter controlled studies are still required for future improvements in affected patients

Zealear D.L., Billante C.L., Chongkolwatana C., and Herzon G.D. (2000) The effects of chronic electrical stimulation on laryngeal muscle reinnervation. ORL J. Otorhinolaryngol. Relat Spec. 62, 87-95.
Abstract: The present study examined the effects of functional neuromuscular stimulation (FNS) on reinnervation of the posterior cricoarytenoid (PCA) muscle. In 4 canines, the recurrent laryngeal nerve (RLN) was sectioned and anastomosed and a patch electrode array implanted for stimulation and recording at multiple PCA sites. Following implantation, FNS was applied to 2 canines for a period of 6 weeks. Two additional animals served as nonstimulated controls. In each animal, histomorphometric analysis of the RLN was used to assess the quality of nerve regeneration and the potential for muscle reconnection. The magnitude of reinnervation was monitored by electromyographic (EMG) potentials evoked by RLN stimulation. The appropriateness of reconnection was determined by the pattern of

spontaneous EMG activity and recovery of vocal fold abduction. Results of this preliminary study indicated that FNS caused an overall repression of reinnervation. However, the repression preferentially inhibited reconnection by foreign nerve fibers, promoting selective reinnervation and preventing synkinesis

Zhao Q., Dahlin L.B., and Kanje M. (1992) Reinnervation of muscles in rats after repair of transsected sciatic nerves with Y-shaped and X-shaped silicone tubes. Muscle reinnervation after nerve repair. Scand. J. Plast. Reconstr. Surg. Hand Surg. 26, 265-270.
Abstract: Reinnervation of the gastrocnemius and anterior tibial muscles was assessed by measurements of tetanic force after repair of sciatic nerves with Y-shaped or X-shaped silicone tubes in rats. The transsected proximal stump of either the tibial or the peroneal fascicle was introduced into the opening of a Y-shaped silicone tube, or both fascicles were introduced into an X-shaped tube. The distal tibial and peroneal fascicles were inserted into the distal outlets of the tubes leaving a gap of 4 mm between proximal and distal stumps. In the X-shaped tubes the proximal inserts were placed opposite or adjacent to their respective distal parts. Sixteen weeks later reinnervation was evaluated by measurements of tetanic force of the gastrocnemius and anterior tibial muscles after electrical stimulation of the fascicles. There was preferential reinnervation in both types of tubes. In Y-shaped tubes about 90% of the tetanic force could be recorded from both muscles after stimulation of the peroneal and tibial fascicles, respectively. Recovery was lower in the X-shaped tubes, amounting to about 75%. Contractions evoked by misrouted fibres were similar (roughly 40%) in both models. We conclude that motor axons preferentially, but not exclusively, selected a path to reinnervate their original target muscle