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, Mao J. Muscle atrophy and procedures for training after spinal cord injury. Phys Ther. 1994;74:50-60.]

Key Words: Electrotherapy, electrical stimulation; Functional training and activities; Muscular activity; Spinal cord injuries.

Spinal cord injuries debilitate thousands of people each year. These injuries are most frequently sustained in automobile accidents; sports activities such as diving, skiing, football, and gymnastics; and, even in peace-time, gunshot. Many of the individuals are young and will depend on external assistance as a substitute for voluntary movement for the rest of their lives. As a result of the considerable advances made in care and rehabilitation in recent years, the life expectancy of the patients who have sustained spinal cord injuries is now only 10% lower than that of nondisabled individuals.

Attempts to replace the central activation of muscle contraction by electrical stimulation of the paralyzed muscles have been made in several rehabilitation centers around the world. Functional electrical stimulation (FES), particularly when combined with external bracing, holds considerable promise as a strategy for assisting patients in executing func-
Several factors must be considered in the application of FES as a means of effective rehabilitation. These factors include (1) the replacement of the central command by the external control, (2) the strength of the bones in the paralyzed limbs, (3) retention of the range of movements of the joints, and (4) the prevention and reversal of muscle atrophy. The external control is provided by the intelligent devices that activate both agonist and antagonist muscles. Movements such as extending an arm require the temporal and spatial activation of muscles normally coordinated by higher brain centers, which rely in part on the sensory feedback from the moving arm. In the absence of the central control and sensory feedback, the external control must be programmed to achieve the same goal by activating muscles at the appropriate time and sequence in order to execute the desired movements. Effective external control has been discussed in detail in recent reviews.4,7,6

Muscles supplied by motoneurons in the spinal cord segments at or below the injury site undergo denervation atrophy as a result of damage to their spinal motoneurons or disuse atrophy as a result of damage to central pathways, with subsequent loss of synaptic input to the muscles’ spinal motoneurons. Muscles are usually referred to as paralyzed in both cases. Muscle force, measured as joint torque in response to external stimulation, may drop to less than 20% to 30%, as compared with the same torque in nondisabled individuals, as a result of disuse atrophy.5 No force will be generated when muscles are completely denervated.

This review focuses on four issues: (1) magnitude of muscle atrophy after spinal cord injuries and the distinction between denervation and disuse atrophies, (2) increased susceptibility of paralyzed muscles to fatigue, (3) capacity of surviving motor nerves to sprout and reinnervate denervated muscle fibers in partially denervated muscles, and (4) effective use of FES to increase the strength and endurance of paralyzed muscles.

**Muscle Atrophy After Spinal Cord Injury**

Since the pioneering work of Tower,18 it has generally been accepted that muscles that are paralyzed as a result of spinal cord injuries undergo atrophy and develop less force. Muscle atrophy, a reduction in the size and/or number of muscle fibers, may be present as denervation atrophy or disuse atrophy.19,20 Denervation atrophy results from injury to motoneurons in the spinal cord or to the motor nerves in the ventral roots through which they exit.5,21 Disuse atrophy occurs as a result of loss of muscle activation due to disruption to the central and segmental synaptic drive onto the surviving spinal motoneurons.5,23-24

**Denervation Atrophy**

With spinal cord injuries, a number of neurons including the motoneurons in the ventral horn may be fatally damaged, and the ventral and dorsal roots may be traumatized even when the cell bodies are not directly affected. Thus, the segmental trauma may lead to substantial denervation of muscles supplied by motoneurons in the spinal cord segment and by motor nerves that exit the spinal cord through the ventral roots at the level damaged.

The muscles that lose all of their innervation undergo drastic and rapid wasting.18-21 Generally, the proportion of muscles that suffer complete denervation after spinal cord injuries is small.22 However, many muscle fibers that receive their innervation from the affected spinal cord segments will suffer partial denervation as a result of the irreversible damage to their motoneurons. For example, in patients with complete lesions at the C-5 to C-6 levels, the paralyzed thenar muscles lose as much as 50% to 90% of their normal complement of motor innervation.23 Prevention or reversal of denervation atrophy in these cases will depend on the capacity of the nerves of surviving motoneurons to sprout and reinnervate as many denervated muscle fibers as possible. The greater the sprouting, the better the reinnervation of denervated muscle fibers. As a result, muscle fibers may survive and contract in response to FES to develop sufficient forces to perform functional movements. Because the remaining motor nerves may not always succeed in reinnervating all the denervated muscle fibers, denervation atrophy may still contribute to the weakness of paralyzed muscles that receive their innervation from spinal segments at or near the lesion site.

Some reports have suggested that there may be a loss of motoneurons several segments below a spinal cord lesion in humans; the loss has been attributed to transsynaptic degeneration of motoneurons.26,27 The issue is not fully settled, however, because several studies28-30 have shown that the number of surviving motoneurons is not significantly reduced. One study26 demonstrated a 20% reduction in the number of motoneurons. Be-
Muscle weights of cat extensor (medial gastrocnemius [MG] and soleus) and flexor (tibialis anterior [TA]) muscles in paralyzed limbs (filled bars) as compared with muscles in the active contralateral limbs (open bars). The spinal cord of the cat was hemisected and unilaterally deafferented. Muscle weights were not different in the MG and TA muscles, but were different in the soleus muscles. The remainder of nerve fibers sprout and reinervate the denervated muscle, denervation atrophy is unlikely to contribute to wasting of muscles that receive their innervation from spinal segments below the lesion site.

Disuse Atrophy

Muscle wasting after spinal cord injury is generally attributed to the muscle inactivity that ensues after loss of the synaptic inputs from higher centers and from spinal cord segments to spinal motoneurons. Studies to date, however, suggest that much of the disuse atrophy of the paralyzed muscles should be attributed to concurrent changes in muscle length or loading conditions, rather than decline in neuromuscular activity. The magnitude of disuse atrophy varies widely from study to study in both human and animals after spinal cord lesions but does not necessarily correlate with the decline in neuromuscular activity. Neural activity that results in neuromuscular activity is generally reduced after spinal cord lesions but varies considerably depending on the type of lesion and the level of spasticity.

Disuse atrophy is more pronounced in paralyzed muscles that normally bear weight, especially those that cross single joints. These muscles often contain a large proportion of slow fatigue-resistant muscle fibers, which are largely responsible for maintaining posture and bearing weight. For example, the soleus muscle, a postural muscle that extends the ankle, undergoes significant atrophy. In contrast, the atrophy may be negligible in other muscles in the lower limb that do not bear weight or that cross more than one joint. For example, the tibialis anterior (TA) muscle, which flexes the ankle and does not normally contract against resistance, does not normally contract against resistance, does not atrophy as much as the soleus muscle in a number of species, including humans. The medial gastrocnemius (MG) muscle, which crosses both the knee and ankle joints, also undergoes less atrophy than the soleus muscle even though it is a synergist to the soleus muscle. The preferential atrophy of soleus muscles of the cat is illustrated in Figure 1. The ability of paralyzed MG muscles of the cat to develop as much tetanic force as normal muscles is illustrated in Figure 2.

The same principles of preferential atrophy of weight-bearing muscles apply to humans. Non-weight-bearing muscles demonstrate little atrophy when paralyzed. For example, in patients with complete C-5 to C-6 lesions, the paralyzed thenar and TA muscles developed isometric forces very similar to those in nondisabled individuals. In contrast, the quadriceps femoris muscle, which normally lifts the lower limb by extending the knee, shows significant atrophy after spinal cord injuries.

A similar pattern of atrophy of limb muscles is seen after space flight, hind-limb suspension, limb immobilization, or tenotomy, conditions in which muscles undergo shortening contractions that are not resisted by a normal load. These findings also suggest that changes in loading or length of paralyzed muscles after spinal cord lesions are responsible, at least in part, for the atrophy that occurs.

The most severe disuse atrophy occurs in unloaded muscles that are immobilized at a shortened length or tenotomized. Muscle fiber degeneration is particularly widespread in tenotomized muscles that undergo unopposed shortening contractions. The detrimental effects of unopposed shortening contractions must be considered when FES regimens are developed.

Fatigue in Paralyzed Muscles

The ability of muscles to sustain force over time depends on their fiber type composition, their metabolic profile, and the general nutritional and cardiovascular state of the organism. Slow-twitch muscles contain mainly slow oxidative fibers, which do not fatigue readily. Fast-twitch muscles contain a small proportion of the slow fibers and mostly fast fibers, which vary in their oxidative and glycolytic enzyme profiles and their corresponding susceptibility to fa-
Figure 2. Tetanic force of paralyzed medial gastrocnemius (MG) muscles and motor units after spinal cord hemisection and deafferentation in cats. (A) Tetanic extensor muscle torque recorded in response to tetanic stimulation of the MG nerve at different times after the surgery did not change significantly. The MG muscles were later isolated in a final acute experiment for measurement of isometric force. (B) Tetanic force recorded from paralyzed muscles (filled bars) in six cats 237±39 days after hemisection and deafferentation was not significantly different from tetanic force in the contralateral control muscles (open bars). Mean values of isometric tetanic force of units isolated from the paralyzed muscles were not significantly different from the mean of unit forces that were measured in normal muscles in unoperated control cats. The filled bars show the data for the paralyzed muscles, and the open bars show the data for the control muscles.

Fatigue-resistant units contain fibers with high oxidative and low glycolytic enzyme activities; fast fatigable units have low oxidative capacity and high glycolytic enzyme activities. Fast-fatigue-resistant units contain fibers with high oxidative and low glycolytic enzyme activities; fast-fatigue-resistant units contain fibers with high oxidative and low glycolytic enzyme activities; fast-fatigue-resistant units contain fibers with high oxidative and low glycolytic enzyme activities. In the cat MG muscle, for example, tetanic force declines to 33% of initial values during repetitive activity (Fig. 3); the remaining force generated by the fatigued muscle corresponds well with the proportion of the total tetanic force that is generated by the slow-fatigue and fast-fatigue-resistant motor units in the MG muscle (Fig. 4).

In patients or animal models of spinal cord injuries, the capacity of paralyzed muscles to sustain contractions is dramatically reduced. This effect of spinal cord injury on muscle endurance is illustrated in an animal model of spinal cord injury in Fig. 4. Within 4 minutes of repetitive activity, the tetanic force of paralyzed muscles declines to 3% of initial values as compared with 33% in the contralateral control muscles. The increased susceptibility to fatigue is accounted for by a reduced number of fatigue-resistant motor units in the paralyzed muscles (Fig. 5), which, in turn, reflects a reduction in oxidative capacity of the muscle fibers.

Disuse atrophy and low endurance in paralyzed muscles in patients with spinal cord injuries makes effective and safe use of FES problematic unless the muscles are adequately prepared by some training protocols and used under the commands of the appropriate external control. For example, the fatigable quadriceps femoris muscle must be adequately trained in order for the patient to stand up safely with a control strategy that will reduce the duration of stimulation.

Sprouting In Partially Denervated Muscles

Reversal of denervation atrophy in a partially denervated muscle depends on how many motoneurons survive the spinal cord injury and their ability to increase the number of muscle fibers that they supply by sprouting. Sprouting occurs from the terminal regions of the intramuscular nerve branches and serves to reinnervate denervated muscle fibers that lie nearby. Normally, motoneurons innervate hundreds or even thousands of muscle fibers. The motoneuron and its muscle fibers form a motor unit. As a result of sprouting, each motoneuron supplies an increased number of muscle fibers, and activation of the motor unit generates more force than normal.

In animal experiments in which the number of muscle fibers per motoneuron or the motor unit force, or both, were recorded, the results showed that motoneurons can supply up to 5 times as many muscle fibers as they normally do (Fig. 5). The details of these studies are described elsewhere. In humans, results of single motor unit recordings show that motoneurons that have survived cervical spinal cord injuries have the
The loss of 97% and 67% of force during the fatigue resistance of partially denervated muscle is left intact, the number of muscle fibers per motoneuron and the muscle fibers they supply are limited to a fivefold increase in functional motor units. This limitation may also account for the inability of nerve sprouts from one muscle to reinnervate adjacent denervated muscles. Muscles that lose all of their innervation are not reinnervated by nerve sprouts belonging to surviving motoneurons that supply other muscles.

The studies discussed show that nerve sprouts from intramuscular nerve branches of surviving motoneurons reinnervate denervated muscle fibers and thereby reduce denervation atrophy. When at least 15% of the normal complement of motor nerves remain, nerve sprouting is a very effective mechanism that compensates for the loss of innervation of many of the muscle fibers and thereby reduces denervation atrophy. As a result, denervation atrophy may be fully reversed in partially denervated muscles and thus the muscles can be activated by FES to generate functional movements.

**Muscle Training for Functional Electrical Stimulation**

Low-frequency (eg, 20-Hz) electrical stimulation via implanted or skin surface electrodes at the motor point has been used in several rehabilitation centers to train muscles prior to application of FES to generate movement. Stimulation has been used to counteract disuse atrophy and low endurance of paralyzed muscles in order for FES to be applied successfully and safely for performance of functional movements.

Training methods vary among centers and for different muscles, particularly with respect to the duration of stimulation, the loading of contracting muscles, and the muscle type. A short stimulation duration and muscle loading regimen is exemplified in a situation in which the subject rides an exercise bicycle that provides loading to the quadriceps femoris muscle while receiving 30 minutes of electrical stimulation daily in three weekly sessions. In other regimens, electrical stimulation is applied for longer periods.
comparisons of the efficacy of different training methods have been difficult.

Low-frequency stimulation paradigms that increase muscle endurance have had different effects on muscle strength, depending on conditions of stimulation. The results of many animal studies in which muscles were stimulated at low frequencies (10-20 Hz) for 2 or more hours per day show that an increase in muscle endurance and oxidative capacity is often accompanied by an undesirable decrease in muscle fiber size and muscle force. For example, endurance of the MG muscle of the cat was dramatically increased by 20-Hz stimulation for 12 hours per day, but the muscle's peak tetanic force was significantly reduced (Fig. 6). These results are consistent with the normal reciprocal relationship between endurance and strength in normal motor units. In human subjects, daily sessions or three sessions per week of low-frequency stimulation increased muscle endurance and strength when the stimulated muscles contracted against set resistances. Muscle strength did not increase significantly under conditions in which the stimulated muscles did not contract against a load (Fig. 7).

Several factors may influence muscle strength and should be considered in designing training regimens, determining their efficacy, and interpreting data derived from many of the animal and human studies. These factors include (1) muscle length, (2) muscle activity, (3) muscle loading, (4) muscle type and function, (5) species, and (6) the interaction of these factors.

Length

Goldspink showed that both innervated and denervated muscles pinned at long length underwent substantially less atrophy initially than muscles fixed at short length. Others have confirmed and extended these original findings. Generally, there is an inverse relationship between the initial degree of atrophy and the

![Figure 4. Cumulative tetanic force of sampled motor units in normal and paralyzed medial gastrocnemius (MG) muscles from six control unoperated cats and six cats in which muscles were paralyzed by spinal cord hemisection and unilateral deafferentation for an average (±SE) of 237±39 days. Tetanic force was measured in 20-50 motor units per muscle, and a total of 350 motor units were ranked in order of their tetanic force and summed to give the cumulative tetanic forces. The fatigue-resistant slow (S) and fast (FR) units generate less force than the more fatigable fast (FI and FF) units. Normally, the S and FR units contribute approximately 30% of the total muscle even though they comprise 50% of the total number of motor units in the MG muscle. After spinal cord injury, the S and FR units contribute about 10% of the total force, and most of the force is generated by the most fatigable fast units, the FF units. The greater fatigability of the paralyzed muscles shown in Figure 5 is accounted for by an increased number of FF units as a result of conversion of FR and FI units into FF units.]

Figures 4 and 5 show the differences in cumulative tetanic force between normal and paralyzed muscles. The figure demonstrates the decrease in the force generated by the S and FR units and the increase in the force generated by the FF units after spinal cord injury.
Salmons and Vrbova\textsuperscript{89} first demonstrated that increased activity could convert fast-twitch muscles to slow-twitch muscles. Their work has been confirmed many times.\textsuperscript{23,80,81,89-92} Using the cat model described in Figures 1 and 2, in which the ipsilateral hind limb is deafferented, Kernell and colleagues\textsuperscript{74-80} were able to greatly reduce the spontaneous nerve activity and study in detail the effects of stimulation on muscle properties. Increased amount of stimulation to the cat peroneus longus muscle induced an increase in fatigue resistance, but a decrease in muscle strength.\textsuperscript{74-78} Superimposing a brief period of high-frequency stimulation (100 Hz for 0.5\% of the day) on continuous low-frequency stimulation (10 Hz for 5\% of the day) prevented most of this loss of strength.\textsuperscript{76} Kernell and colleagues\textsuperscript{75} suggested that the "force stress" provided by the high-frequency tetanic burst favored the maintenance of factors of relevance to contractile force. Recent attempts to reproduce these findings in human subjects, however, have not been successful (DB Popović, unpublished observations).

**Activity**

It is generally accepted\textsuperscript{95-97} that to build strength a muscle must generate close to maximal forces for short periods of time, whereas to improve endurance a muscle must maintain small forces for long periods of time (e.g., sprinting versus long-distance running). Thus, isometric or even eccentric forceful contractions may be necessary for building strength, whereas concentric contractions against light loads may increase endurance. These concepts, taken from sports medicine literature on athletes and nonathletes and from animal studies of exercise and muscle overload, have been applied to the training of paralyzed muscles using FES,\textsuperscript{72,97} but their application still requires rigorous testing.

Figure 5. Tetanic force and number and spatial distribution of muscle fibers in isolated motor units in rat tibialis anterior (TA) muscles under normal conditions (A,C) and under conditions in which remaining motor units sprout and increase motor unit size after partial denervation of the muscle (B,D). Tetanic force and number of muscle fibers in single motor units was measured in (A) control rats and (B) rats in which the L-5 root was cut 4 to 12 months previously under sodium pentobarbitol anesthesia (30 mg/kg) and sterile conditions. Ventral root filaments were exposed in a laminectomy and teased to isolate and record tetanic force of single motor units in the isolated TA muscle after denervation of all other muscles in the hind limb. Glycogen-depleted muscle fibers in one motor unit per muscle were visualized and counted in 10-μ muscle cross sections (camera lucida drawings; C,D). Tetanic force varies as a direct function of number of muscle fibers per motor unit for (A) control and (B) sprouted motor units. (C) The muscle fibers in any one motor unit in normal muscle are intermingled with fibers belonging to several different motor units and show a typical mosaic distribution pattern in a circumscribed unit "territory." (D) Muscle fibers in one unit in partially denervated muscles still occupy a circumscribed area, but the larger-than-normal number of muscle fibers are more densely packed within this area.
**Figure 6.** (A) Contractile endurance (endurance index-tetanic force recorded 2 minutes after tetanic stimulation at 13 pulses at 25 Hz every second for 4 minutes relative to tetanic force at 0 minutes), (B) contractile speed (contraction time-time to peak twitch force), and (C) contractile strength (isometric tension developed in response to 100-Hz stimulation normalized to tension developed by the muscles prior to onset of daily electrical stimulation) of medial gastrocnemius (MG) muscles plotted as a function of time of daily 20-Hz, 24-hour stimulation in a 50% duty cycle (2.5 seconds on-2.5 seconds off). The data for each of eight muscles are plotted with separate symbols. In each animal, cuff electrodes were implanted and the wires were externalized for attachment to an external stimulator that was mounted on the cat's back in a hexelate basket. The effects of chronic stimulation were monitored at regular intervals by recording extensor muscle torque evoked by stimulation of the MG nerve via the cuff electrode under halothane anesthesia. Each muscle thus served as its own control. As the lever arm was the same for all measurements, torque has been referred to as muscle tension.

**Muscle Type and Function**

As previously described, a general finding in both patients with spinal cord injuries and animal models is the more severe atrophy of extensor muscles, especially slow-twitch muscles that cross a single joint. These muscles are largely responsible for maintaining posture and bearing weight. In patients, the quadriceps femoris muscle (a knee extensor) undergoes more significant atrophy than the TA muscle (a fast-twitch ankle flexor). The strength of the quadriceps femoris muscle does improve after retraining, and the strength of the TA muscle changes very little.

**Species**

The speed at which muscles contract varies widely among species. For the same muscle in the species commonly studied, contractile speed will generally follow the following descending order: mouse→rat→cat→human. Differences in muscle contractile speed are associated with differences in the proportions of fast and slow muscle fibers in the same muscles across species. In addition, differences in muscle strength and endurance are associated with the differences in the fiber type composition. Thus, one cannot assume that data from experiments on rodents, for example, will automatically apply to human subjects. Thus, parallel experiments in both human and nonhuman muscles may provide insight into preparation of muscles for FES regimens. Differences in the resting length of paralyzed muscles in patients and animals must also be taken into account in assessing efficacy of training with FES. For example, patients with spinal cord injuries sitting in wheelchairs much of the day usually keep their ankles at approximately a right angle, whereas a spinalized cat will fully extend the paralyzed hind limb by dragging it. Thus, species differences must be taken into account in comparisons of the outcome of stimulation protocols.
Muscles undergo atrophy after spinal cord injury. In muscles that receive their innervation from spinal cord segments at or close to the lesion site, denervation atrophy may be extensive. Nerve sprouting from the intramuscular branches of the surviving motoneurons is very effective in reducing the atrophy in partially (but not completely) denervated muscles. Muscles that are paralyzed by loss of central and segmental input to their motoneurons and not by denervation undergo disuse atrophy. Weight-bearing muscles, particularly those that cross a single joint, are most susceptible. Several factors are likely to contribute to disuse atrophy including changes in muscle length, loading, and activity, all of which vary with muscle type and function. These factors should be systematically controlled in the development and use of electrical stimulation protocols for preparing muscles prior to the application of FES to elicit functional movements.

Conclusions

Muscles lose weight and are less forceful even if they are exercised or stimulated for 20 minutes per day; the muscles are only able to maintain weight and force if they are passively stretched by changing joint angle. Physiological extensors that maintain body posture against gravity are activated more frequently than flexors. Thus, it is not surprising that spinalization has a much more drastic impact on the activity of extensors with correspondingly greater changes in their fiber type proportions than that of the flexors. Shortening contractions in unloaded muscles will induce fatigue more rapidly than isometric contractions because more oxygen is consumed (Fenn effect). Thus, changes in muscle properties in any case could be due to the combined effects of load, length, and phosphate metabolism.

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