INVITED REVIEW

ABSTRACT: This review provides a comprehensive overview of the clinical uses of neuromuscular electrical stimulation (NMES) for functional and therapeutic applications in subjects with spinal cord injury or stroke. Functional applications refer to the use of NMES to activate paralyzed muscles in precise sequence and magnitude to directly accomplish functional tasks. In therapeutic applications, NMES may lead to a specific effect that enhances function, but does not directly provide function. The specific neuroprosthetic or "functional" applications reviewed in this article include upper- and lower-limb motor movement for self-care tasks and mobility, respectively, bladder function, and respiratory control. Specific therapeutic applications include motor relearning, reduction of hemiplegic shoulder pain, muscle strengthening, prevention of muscle atrophy, prophylaxis of deep venous thrombosis, improvement of tissue oxygenation and peripheral hemodynamic functioning, and cardiopulmonary conditioning. Perspectives on future developments and clinical applications of NMES are presented.

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NEUROMUSCULAR ELECTRICAL STIMULATION IN NEUROREHABILITATION

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This article provides a comprehensive review of the clinical uses of neuromuscular electrical stimulation (NMES) in neurological rehabilitation. NMES refers to the electrical stimulation of an intact lower motor neuron (LMN) to activate paralyzed or paretic muscles. Clinical applications of NMES provide either a functional or therapeutic benefit. Moe and Post[207] introduced the term functional electrical stimulation (FES) to describe the use of NMES to activate paralyzed muscles in precise sequence and magnitude so as to directly accomplish functional tasks. In present-day applications, functional tasks may include standing or ambulatory activities, upper-limb performance of activities of daily living, and control of respiration and bladder function. A neuroprosthesis is a device or system that provides FES. Accordingly, a neuroprosthetic effect is the enhancement of functional activity that results when a neuroprosthesis is utilized. NMES is also used for therapeutic purposes. NMES may lead to a specific effect that enhances function but does not directly provide function. One therapeutic effect is motor relearning, which is defined as "the recovery of previously learned motor skills that have been lost following localized damage to the central nervous system."[180] Evolving basic science and clinical studies on central motor neuroplasticity now support the role of active repetitive-movement training of a paralyzed limb. If active repetitive-movement training facilitates motor relearning, then NMES-mediated repetitive-movement training may also facilitate motor relearning. Other examples of therapeutic applications include treatment of hemiplegic shoulder pain, cardiovascular conditioning, treatment of spasticity, and prevention of muscle atrophy, disuse osteoporosis, and deep venous thrombosis (DVT).

This review focuses on the clinical uses of NMES for functional and therapeutic applications in patients with spinal cord injury or stroke. In order to provide a foundation for the various clinical applications, the neurophysiology of NMES and compo-

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Abbreviations: ANN, artificial neural network; DVT, deep venous thrombosis; ECU, external control unit; EMG, electromyography; FES, functional electrical stimulation; Fint, fatigue-intermediate; FR, fatigue-resistant; LMN, lower motor neuron; LSU-RGO, Louisiana State University Reciprocating Gait Orthosis; LTP, long-term potentiation; MHC, myosin heavy chain; MRI, magnetic resonance imaging; NMES, neuromuscular electrical stimulation; PG/PS, pattern generator / pattern shaper; PID, proportional integral derivative; RF, radiofrequency; ROM, range of motion; SCI, spinal cord injury; TENS, transcutaneous electrical nerve stimulation; UMN, upper motor neuron

Key words: bladder function; functional electrical stimulation; motor relearning; neuromuscular electrical stimulation; neuroprosthesis; rehabilitation; respiratory control; spinal cord injury; stroke

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nents of NMES systems are briefly reviewed. The specific neuroprosthetic or "functional" applications include upper- and lower-limb motor movement for self-care tasks and mobility, respectively, bladder function, and respiratory control. Specific therapeutic applications include poststroke motor relearning as well as the examples mentioned earlier. Lastly, perspectives on future developments and clinical applications of NMES are presented.

NEUROPHYSIOLOGY OF NMES

NMES is initiated with the excitation of peripheral nervous tissue. The mathematical characterization of neuronal action potential generation is largely predicated on the seminal work of scientists and neurophysiologists including Galvani,[106] Lapicque[175] and Hodgkin and Huxley.[130] More recently, McNeal[200] mathematically defined the time course of events following stimulus application to the propagation of the action potential in a normal healthy myelinated nerve. The term "stimulus threshold" defines the lowest level of electrical charge that generates an action potential. The "all or none" phenomenon of the action potential produced by natural physiologic means is identical to the action potential induced by NMES.

Conduction of impulses in a nerve is influenced considerably by the nerve's cable properties. Hodgkin and Rushton in 1946[131] used extracellular electrodes to measure applied current along lobster axons to describe the spread of current along nerve fibers of uniform diameter composed of a central conductor and insulating sheath. Nerve fiber recruitment and resultant force characteristics of muscle contraction are modulated by both stimulus pulse width[277] and stimulus frequency.[3] Other variables include distance from the stimulating electrode and membrane capacitance. The threshold for eliciting a nerve fiber action potential is 100 to 1,000 times less than the threshold for muscle fiber stimulation.[209] Thus, clinical NMES systems stimulate either the nerve directly or the motor point of the nerve proximal to the neuromuscular junction.

The nerve fiber recruitment properties elicited by NMES differ from those elicited by normal physiologic means. An action potential produced by normal physiologic mechanisms initially recruits the smallest-diameter neurons prior to recruitment of larger-diameter fibers, such as alpha motor neurons.[127] Rushton[248] was one of the first researchers to examine the theoretical relationship between fiber diameter and conduction velocity. Hodgkin[132] proposed that the velocity of action potential propagation should vary directly with the square root of the fiber diameter. The Henneman size principle of voluntary motor unit recruitment described this progressive size-dependent recruitment of motor units.[128] Arbuthnott et al.[9] examined in detail this relationship between fiber diameter and conduction velocity in peripheral nerve. The nerve fiber recruitment pattern mediated by NMES follows the principle of "reverse recruitment order" wherein the nerve stimulus threshold is inversely proportional to the diameter of the neuron. Thus, large-diameter nerve fibers, which innervate larger motor units, are recruited preferentially. Recent work by Lertmanorat and Durand[183] proposes the clinical applicability of a reshaping of the extracellular voltage that may allow the reversal of the "reverse recruitment order" elicited by NMES.

NMES is dependent on an intact (alpha) LMN. Several studies document the therapeutic benefit of electrical stimulation on muscle-fiber regeneration in LMN denervation[50,149,280]; however, the clinical application of NMES is presently limited to neurologic injuries involving the upper motor neuron (UMN) such as spinal cord injury (SCI), stroke, brain injury, multiple sclerosis, and cerebral palsy. NMES is delivered as a waveform of electrical current characterized by stimulus frequency, amplitude, and pulse width. The amplitude and pulse width determine the number of muscle fibers that are activated.[209] Temporal summation is determined by the rate at which stimulus pulses are applied to muscle. The strength of the resultant muscle contraction is modulated by adjustment of the stimulus parameters. The minimum stimulus frequency that generates a fused muscle response is ~12.5 Hz. Higher stimulus frequencies generate higher forces but result in muscle fiber fatigue and rapid decrement in contractile force. An optimal NMES system utilizes the minimal stimulus frequency that produces a fused response.[26,173,200] Ideal stimulation frequencies range from 12–16 Hz for upper-limb applications and 18–25 Hz for lower-limb applications (frequency range for NMES systems is 10–50 Hz). Greater muscle force generation is accomplished by either increasing the pulse duration (typically 200 μs) or stimulus amplitude to activate neurons at a greater distance from the activating electrode. Parameters for safe stimulation for implanted NMES systems have been established experimentally.[209]

The clinical application of NMES systems is complicated by the fact that the contractile force of muscle is highly nonlinear and variable over time. Muscle force generation is also impacted by multiple factors distinct from the stimulation parameters of the NMES system. These factors include the inherent length–ten-

sion characteristics of the muscle, impact of the joint angle on changes in the tendon arm moment arm, and volume conduction of the current that may recruit muscles beyond the targeted muscle.[115,153]

Skeletal muscle contains "fast" and "slow" muscle fibers that are distinguished on the basis of contraction kinetics. These fiber types are generally categorized according to the specific myosin heavy chain (MHC) isoforms that they express.[104,144] Histochemical analysis led to the original designations of types I and II muscle fibers. Slow-twitch, oxidative type I fibers generate lower forces, but are fatigue resistant; fast-twitch glycolytic type II fibers generate higher forces but fatigue more rapidly. Muscle fibers are typed using histochemical staining for myosin ATPase, MHC isoform identification, and biochemical identification of metabolic enzymes. Myosin ATPase histochemistry energy metabolism distinguishes the muscle fibers that comprise a motor unit, all of which exhibit similar contractile and fatigue characteristics. Motor units are thus classified based on fiber type contractile characteristics as either slow-twitch (S) or fast-twitch (F). The F motor units are classified as either fast-twitch fatigue-resistant (FR), fast-twitch fatigue-intermediate (Fint), or fast-twitch fatigable (FF).[256]

An alteration in functional demands result in conversion of muscle fiber types via altered gene expression, changes in the expression of contractile proteins and metabolic enzymes,[35] and adaptations in the cellular electrophysiologic properties (expression or function of ion channels).[171,312] Disuse muscle atrophy common in an UMN injury is characterized by conversion of type I muscle fibers to type II fibers.[242] An ideal application of NMES allows preferential stimulation of fatigue-resistant type I fibers. However, NMES systems preferentially recruit type II fibers due to lower stimulation thresholds. Chronic electrical stimulation facilitates reversal of fiber type conversion secondary to motor unit plasticity.[224] This reversal of fiber type conversion may be related to the motor neuron firing patterns that control expression of contractile proteins and metabolic enzymes in muscle fibers during electrostimulation.[172]

SYSTEM COMPONENTS

Most clinically available NMES systems fall into two broad categories: transcutaneous (surface) and implanted (percutaneous, epimysial, epineural, intraneural, and cuff) systems. NMES systems are either voltage- or current-regulated. Despite the variable motor response, voltage-regulated stimulation is more common with transcutaneous NMES systems; as impedance (resistance) increases due to electrode–skin interface changes, current is decreased. Current density as opposed to absolute voltage determines the potential for tissue injury. Due to less variability in resistance and the need for muscle contraction consistency and repeatability, constant-current applications are more common in implanted NMES systems.

Electrode type impacts on potential for tissue injury and efficacy of intervention. The simplest electrode is the transcutaneous electrode that is applied to the skin and stimulates directly over the peripheral nerve or motor point. The motor point is the muscle location that exhibits the most robust contraction at the lowest level of stimulation. All transcutaneous electrodes use external leads that connect to a stimulator. Two electrodes placed in either a monopolar or bipolar configuration are required to produce an electrical current flow. The active electrode is placed directly over the peripheral nerve or motor point; the indifferent electrode is placed either on fascia or a tendinous insertion (monopolar) or near the active electrode (bipolar). Bipolar stimulation creates a more localized electrical field, which may result in greater selectivity of muscles.[115] Transcutaneous electrodes pose a risk of tissue injury, particularly in patients with concomitant sensory or cognitive deficits. Activation of cutaneous pain receptors, difficulties in positioning, poor selectivity, insecure fixation on moving limbs, skin irritation, and cosmetic factors are common limitations of transcutaneous electrodes. Although a constant-voltage transcutaneous NMES system minimizes the risk of high current densities associated with tissue–electrode interface fluctuations, variability in muscle stimulation and inconsistent functional response can result. Transcutaneous electrodes are more commonly used for therapeutic applications.[22]

The minimally invasive percutaneous intramuscular electrode[201] reduces the risk of tissue injury yet poses other safety issues, including the risk of displacement or breakage associated with anchoring of the external lead and electrode-related infection and granuloma formation secondary to retained electrode fragments. The cumulative failure rate of percutaneous electrode varies between 56% and 80%,[160,202,261] which limits the use of a percutaneous electrode to less than 3 months. Other researchers have demonstrated lower failure rates with the use of ultrafine percutaneous electrodes.[124,255] All percutaneous electrodes connect to lead wires that exit the skin and connect to the stimulator. The advantages of the percutaneous electrode are the elimination of skin resistance and cutaneous pain issues, greater

muscle selectivity, and lower stimulation currents. Percutaneous electrodes are particularly usefully in activating small, deep muscles such as the intrinsic muscles of the hand. For intramuscular electrode applications, safe stimulation parameters include charge balanced, biphasic pulses with amplitudes of 20 mA, and frequencies ranging from 10–50 Hz.[209]

Surgically implanted electrodes designed for long-term use include epimysial, epineural, intraneural, and helix (cuff) electrodes. These electrodes all require open surgical procedures. They connect to implanted lead wires and require the implantation of a stimulator that receives power and command instructions through a radiofrequency (RF) telemetry link to an external control unit (ECU). Epimysial electrodes are sutured directly to the epimysium or fascia of the target muscle.[115,300] They are particularly useful for activation of broad, superficial, or thin muscles.[152,287] Nerve-based electrodes are indicated depending on location and recruitment requirements of the target muscle.[223] Epineural electrodes are sutured to connective tissue directly surrounding the nerve; intraneural electrodes that penetrate to the intrafascicular bundles[33,133,210] are presently limited to research applications. Direct nerve stimulation is most commonly achieved via a nerve cuff electrode which, by encompassing the nerve trunk, requires approximately one-tenth of the current necessary for intramuscular stimulation.[145,211,273,276] Nerve cuff electrodes are safe and effective.[111,154,301] Complications of nerve cuff electrodes include mechanical irritation at the cuff–nerve interface and tissue growth with resultant nerve compression or blockage.[211]

There are a number of safety and biocompatibility issues related to implanted electrodes utilized in various NMES systems.[4,176] Development of the ideal electrode requires minimizing issues of lead and electrode breakage, variability in electrode placement, nerve–electrode interface complications, surgical invasiveness, and optimization of stimulus parameters to generate sufficient sustained, predictable motor force. Although NMES systems are characterized by the peripheral nerve–electrode interface, research is increasingly focusing on new technologies such as harnessing cortical control signals that may provide an enhanced means of interfacing with a neuroprosthesis to facilitate functional movement.[178]

For neuroprostheses, there is the added requirement of volitional control to carry out specific functional tasks. FES control system design presents a significant challenge to correlate user intent to functional performance. An open-loop muscle activation control pattern is characterized by a preset pattern of neuromuscular stimulation. Most clinical FES systems employ open-loop control with sensory feedback limited to residual visual and proprioceptive input. A closed-loop control system allows for continuous real-time modification of the stimulation pattern based on sensory feedback. Given the nonlinear and temporal variability of contractile muscle force, a closed-loop system modulated by sensor-derived feedback signals offers clear advantages. There are a number of potentially reliable sources of control signals including biomechanical sensors,[49,64,236] tilt sensors,[74] accelerometers,[195,257,285] gyroscopes,[257,285] myoelectric control,[296] artificial neural networks (ANNs),[98] pattern generator/pattern shaper (PG/PS) controllers,[240] biopotentials[259] via neural cuff recordings,[232,275] a proportional integral derivative (PID) controller,[237] and brain cortical activity.[134] An optimal FES control system allows for consistent and predictable response to external perturbations including changing muscle loads and internal time variations such as fatigue. Specific control systems employed in available neuroprostheses systems are presented later in this review.

A special case of an electrode/stimulator system that does not fit well into the traditional classification scheme is the injectable microstimulator,[10,302,303] which is presently undergoing clinical trials for various applications. The device is no more than 2 cm long and functions as stimulator, electrode, and receiver. The individually addressable microstimulator is injected into or near the target tissue via a minimally invasive procedure. The target tissue is within the muscle or soft tissue contiguous to a specific nerve or motor point. The first-generation device was glass-encased with an external tantalum capacitor electrode. A second-generation device is designed to be more durable and less susceptible to mechanical and electrostatic trauma.[10] The device receives power and digital command data via a single external RF coil and generates stimulation pulses of 0.2–30 mA at 4–512 μs pulse duration. A battery-powered microstimulator is presently under development.

NEUROPROSTHESES

Upper-Limb Applications. ***Spinal Cord Injury.*** Neuroprostheses can provide grasp and release function for individuals with a complete SCI at the cervical level to facilitate activities of daily living. The majority of upper-limb neuroprostheses are targeted for individuals with C5 and C6 motor levels. Neuroprostheses can be applied to a limited extent to the C4 motor level, but there are no clinically deployable

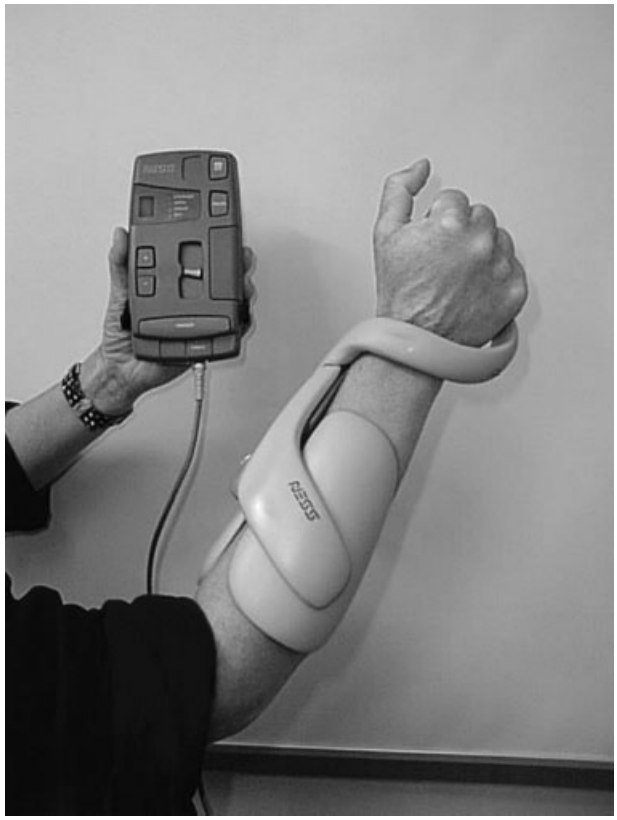

FIGURE 1. A hybrid brace-transcutaneous neuroprosthesis system that is worn on the hand and forearm. The exoskeleton positions the wrist in a functional position and the five transcutaneous electrodes built into the exoskeleton stimulates specific muscles to provide coordinated hand opening and closing. (NESS H200, courtesy of Bioness Inc., Santa Clarita, CA.)

systems for this population to date. For individuals with C7 or C8 motor levels there are other treatment options (such as tendon transfers) that can provide considerable enhancement of function.

All existing upper-limb neuroprostheses consist of a stimulator that activates the muscles in the upper limb, an input transducer, and a control unit. The control signal for grasp is derived from retained voluntary function. For example, a person with C5 complete tetraplegia usually has the ability to retract and protract the shoulder. A shoulder position transducer can detect this movement to generate a command signal for hand opening and closing. The user typically has control over electrically stimulated gross hand grasp opening and closing, but does not have direct control over the activation of each muscle, thus simplifying the control task required by the user.

A hand neuroprosthesis system developed in Ra'anana, Israel, incorporates transcutaneous electrodes into a brace for hand grasp and release (Fig. 1). The brace fixes the wrist in neutral, making it applicable primarily to persons with C5 complete tetraplegia who do not have a tenodesis grasp. In a clinical study, Snoek et al.[264] evaluated 10 individuals with C5/C6 tetraplegia for fitting of the neuroprosthesis, and four participated in the functional training portion of the study. These four subjects performed at least two tasks independently using the device that they could not perform otherwise. Three of the subjects demonstrated improvement in pouring from a can and opening a bottle. Other improved tasks include shaving, putting on socks, and handling a hammer. The system has Food and Drug Administration (FDA) approval in the United States and the CE marking ("Conformite Europeene," health, safety, and environmental protection designation) in Europe.

Handa and Hoshimiya,[123] of Sendai, Japan, developed a percutaneous neuroprosthesis system that uses up to 30 percutaneous electrodes to provide palmar, lateral, and parallel extension grasp patterns. Percutaneous systems address the problems of specificity and repeatability encountered with transcutaneous stimulation systems. The implantation is minimally invasive, requiring needle insertion only with no surgical exposure. Grasp opening and closing are controlled by a switch operated by the opposite arm or by respiration using a sip/puff type of control. The system is available primarily in Japan. However, there are no studies that formally assess outcomes with respect to disability and user satisfaction.

In 1986, Peckham et al.[221] in Cleveland, Ohio, implemented the first implanted hand neuroprosthesis (Fig. 2). The system consists of 8 implanted electrodes and an implanted receiver-stimulator unit, providing lateral and palmar grasp for persons with C5 and C6 complete tetraplegia.[260] An RF inductive link provides the communication and power to the implant receiver-stimulator. The proportional control of grasp opening and closing is achieved using shoulder motion, which is measured using an externally worn joystick on the chest and shoulder.[142] The implantable system has FDA approval in the United States and the CE mark in Europe.

Of the three commercialized devices, the implanted system underwent the most extensive assessment of functional outcomes. A multicenter clinical trial evaluating 50 individuals with C5 or C6 SCI implanted with the upper-limb neuroprosthesis showed significant reduction in impairments and activity limitations.[222] More than 90% of participants are satisfied with the neuroprosthesis, and most use it regularly. Follow-up surveys indicated that usage patterns are maintained for at least 4 years postimplant.[308] Adverse events due to the implanted com-

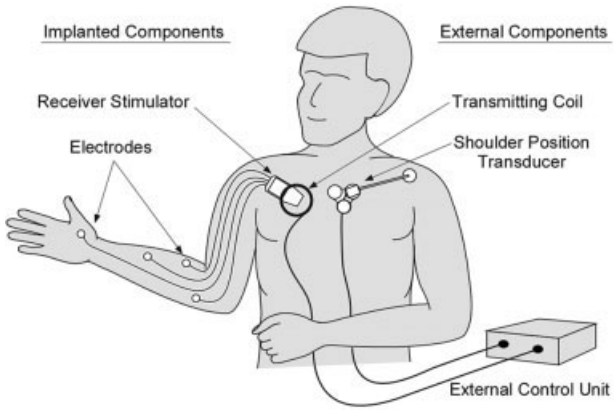

FIGURE 2. Schematic of the implantable hand neuroprosthesis system for tetraplegia. The system provides lateral and palmar grasp in response to activation of a shoulder-position transducer. The RF link provides the communication between the external control unit and the implanted stimulator. (Reproduced with permission. Chae et al. In: DeLisa J, editor. Physical medicine and rehabilitation: principles and practice. Philadelphia: Lippincott Williams & Wilkins, 2005. p 1405–1426. © 2005 Lippincott Williams & Wilkins.)

ponents and surgical installation are few. The infection rate is less than 2%. There are no cases of neuroprosthesis failure and less than 1% lead failures. Although the device is safe and clinically effective, the system is no longer commercially available. Reasons for this are complex and beyond the scope of this review. Cost, limited market, function limited to the hand, and insufficient "buy-in" by the rehabilitation community are all possible contributory factors.

New research in upper-limb neuroprostheses focuses on stimulation of additional muscles, implementation of new control methods, and incorporation of advanced technologies in order to broaden clinical indications and facilitate clinical implementation. Stimulation of triceps,[43] pronator quadratus,[182] and finger intrinsics[177] increases work space and enhances overall upper-limb and hand function. The incorporation of alternative command source strategies including wrist position,[125] activation of voluntary antagonists to control elbow angle and forearm supination/pronation,[182] myoelectric signal from either forearm or neck muscles,[159] and cortical control[306] are under investigation. The incorporation of advanced technologies such as implanted control transducers,[143] new electrode technology,[118] and use of devices that minimize surgical invasiveness[190] may further facilitate clinical implementation and enhance effectiveness. Finally, studies demonstrate the feasibility of neuroprostheses for high tetraplegia (C2–4).[23,122]

Stroke. In view of the success of the hand neuroprosthesis in tetraplegia,[222] it is reasonable to apply the technology to persons with hemiplegia. However, review of the literature reveals only five full-length publications in English-language peer-reviewed journals that evaluate the effectiveness of a hand neuroprosthesis for enhancing the upper-limb function of stroke survivors. Two reports utilized customized transcutaneous electrical stimulation systems,[203,238] two utilized the previously described transcutaneous electrical stimulation-brace hybrid system,[5,6] and one utilized a percutaneous intramuscular electrical stimulation system (Fig. 3).[58] All studies used limited sample sizes and open-label designs with performance evaluated with and without the neuroprosthesis.

These reports share several common themes. The ability of the neuroprostheses to provide clinically relevant improvement is limited to a small number of selected functional tasks. When the limb is in a resting position, the various systems open and close the hand without difficulty. However, when patients are asked to perform a specific functional task a great deal of mental and physical effort is required, which is often associated with an increase in generalized hypertonia. In the face of increased hypertonia, neuroprostheses do not open the hand effectively or reliably.

At the present time a clinically viable hand neuroprosthesis system is not available for persons with hemiparesis and additional research is required. A

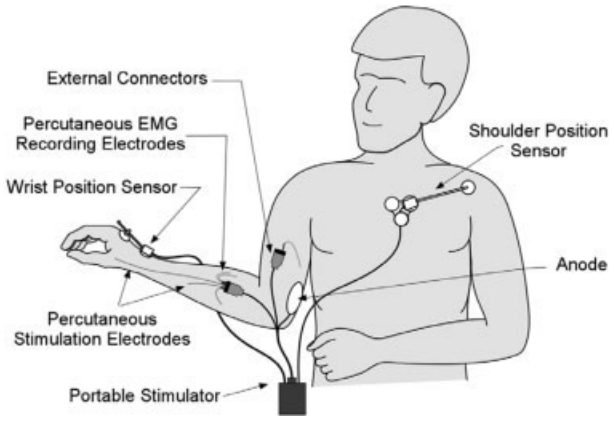

FIGURE 3. Schematic of a percutaneous hand neuroprosthesis system for hemiplegia. The RF link with the stimulator shown in Figure 2 is now replaced by direct percutaneous connection. Three control options of shoulder transducer, wrist joint angle transducer, and EMG controller are illustrated. However, only one control method is used at any one time. (Reproduced with permission. Chae J, Hart R. Neurorehabil Neural Repair 2003; 17:109–117. © 2003 SAGE.)

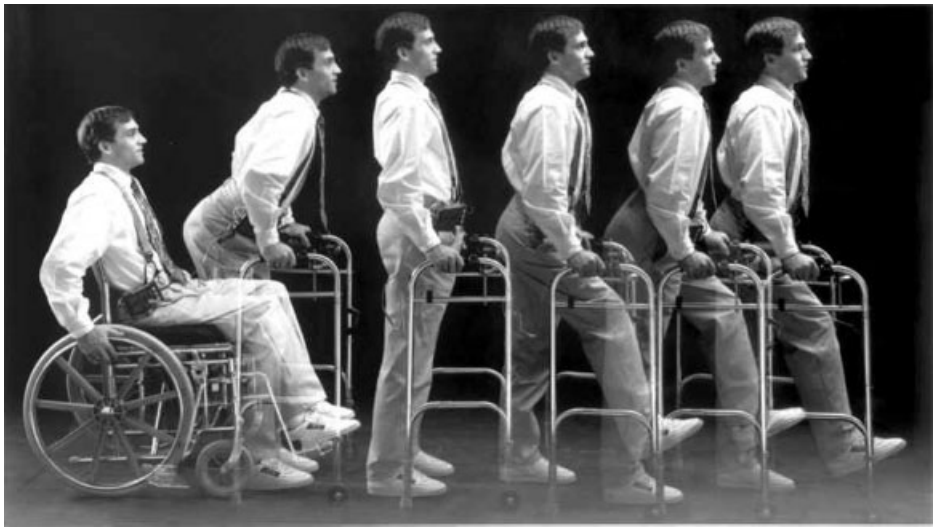

FIGURE 4. A transcutaneous multichannel neuroprosthesis system allows persons with paraplegia unbraced ambulation for home and short community distances. (Parastep I System User, courtesy of Sigmedic Inc., Fairborn, OH.)

clinically deployable system must demonstrate the ability to: (1) facilitate bilateral tasks, (2) provide proximal and distal control, (3) have sufficient miniaturization to not interfere with ambulation, (4) utilize control paradigms that produce effortless movement of the impaired upper limb without compromising the function of the intact limb, and (5) "turn off" overactive muscles as well as stimulate weak muscles.[58]

Lower-Limb Applications. *Spinal Cord Injury.* Multichannel transcutaneous electrical stimulation systems are successful in producing standing and stepping for persons with complete SCI. These systems are relatively simple, consisting of 2–6 channels of continuous stimulation.[116,140,168,310] Systems employing percutaneous intramuscular electrodes allow for more complex movements[196] and can provide simple mobility and one-handed reaching tasks.[162,286] A cochlear implant modified to stimulate motor neurons[78] and a 12-channel system for activation of the L2-S2 motor roots[86] have been used for exercise and standing in a limited number of volunteers. For long-term clinical application, implanted systems such as these provide major advantages over transcutaneous and percutaneous systems including convenience, cosmetic benefit, reliability, and repeatability.

The pioneering work in the application of neuroprostheses for restoration of standing and walking for individuals with complete and incomplete SCI conducted in the 1970s and 1980s continues to be employed in many laboratories and clinics around the world.[14,168] Standing is achieved by simultaneously activating both sets of quadriceps in response to a command input. A stride is produced by maintaining activation to the quadriceps of the stance leg while initiating a flexion withdrawal in the contralateral limb.[155,295] To complete the stride, activation of the knee extensors on the swinging limb is initiated while the reflex is still active and flexing the hip. These implementation procedures for standing and stepping with transcutaneous stimulation are incorporated in a system that has FDA approval (Fig. 4).[105,116] However, complicating issues include poor standing posture due to hip flexion generated by the rectus femoris when the quadriceps are stimulated, lack of or habituation of a strong flexion withdrawal reflex, and difficulty in controlling the swing limb motion due to the mass flexion response of the reflex.

With the assistance of the neuroprosthesis, many persons with neurologically incomplete spinal cord lesions can become functional ambulators because some degree of motor, sensory, and proprioception function is preserved. NMES augment muscle contraction increases stride length and reduces physiologic cost index during walking. In some patients exaggerated extensor tone provides safe standing, but does not facilitate step initiation. In these patients peroneal nerve stimulators may inhibit extensor tone and help to initiate a step.[13,169] When necessary, hip abductors, hamstrings, and trunk extensors are included in the stimulation patterns.[114] Nevertheless, the high neurologic variability of the incomplete SCI population requires caution in the application of neuroprostheses.

These approaches have implications for implanted lower-limb systems. However, implanted systems activate individual muscles rather than relying on the flexion withdrawal reflex or extensive bracing. Complex lower-limb motions are synthesized by activating up to 48 separate muscles with chronically indwelling percutaneous intramuscular electrodes. Some well-trained subjects are able to walk 300 m repeatedly at 0.5 m/s with this system.[163] However, implanting and maintaining a system consisting of a large number of percutaneous electrodes is not practical. Therefore, implantable receive-stimulators are used as a platform for clinical trials of walking system for persons with complete and incomplete thoracic SCI. A multicenter clinical trial of a lower-limb neuroprosthesis system that utilizes a single implanted 8-channel device for standing and transfers is presently under way.[77] A 16-channel lower limb implanted system is also presently under investigation (Fig. 5).[165]

Hybrid systems employing various brace and stimulation components are reliable and relatively simple to implement in clinical environments with orthotic and prosthetic fabricating capacity. These systems are fitted to patients with complete or incomplete paraplegia.[146,197,265,266] One design combines a Louisiana State University Reciprocating Gait Orthosis (LSU-RGO) with a 4-channel transcutaneous stimulator and a flexible copolymer electrode cuff. Follow-up studies on RGO-based hybrid orthoses show that up to 41% of system recipients use it for gait[101] and 66% use it for exercise.[267] Standing with the knee joints of the brace locked allows stimulation to be discontinued, thus postponing the onset of fatigue. The orthotic components of these systems may also protect the insensate joints and osteoporotic bones of users with long-standing SCI from possible damage resulting from the loads applied during weight-bearing and ambulation. Other more recent developments include hybrid FES with a medial-linkage knee–ankle–foot orthosis,[254] energy storage orthosis,[90] more energy-efficient and cosmetically accepted hip–knee–ankle orthosis,[206,251] and implantable multichannel FES with trunk–hip–knee–ankle foot orthosis.[164]

In summary, the inherent value of lower-limb neuroprosthesis systems for persons with SCI in their current forms is in the ability to provide short-duration mobility-related tasks, such as overcoming physical obstacles or architectural barriers and exercise. The literature suggests that ambulation with lower-limb neuroprosthesis is an option for short distances but is unlikely to be an alternative to a wheelchair. The metabolic energy currently required to walk with a neuroprosthesis is too high to make it a practical alternative to the wheelchair for long-distance transportation over level surfaces, although this remains a worthwhile and achievable long-term goal.

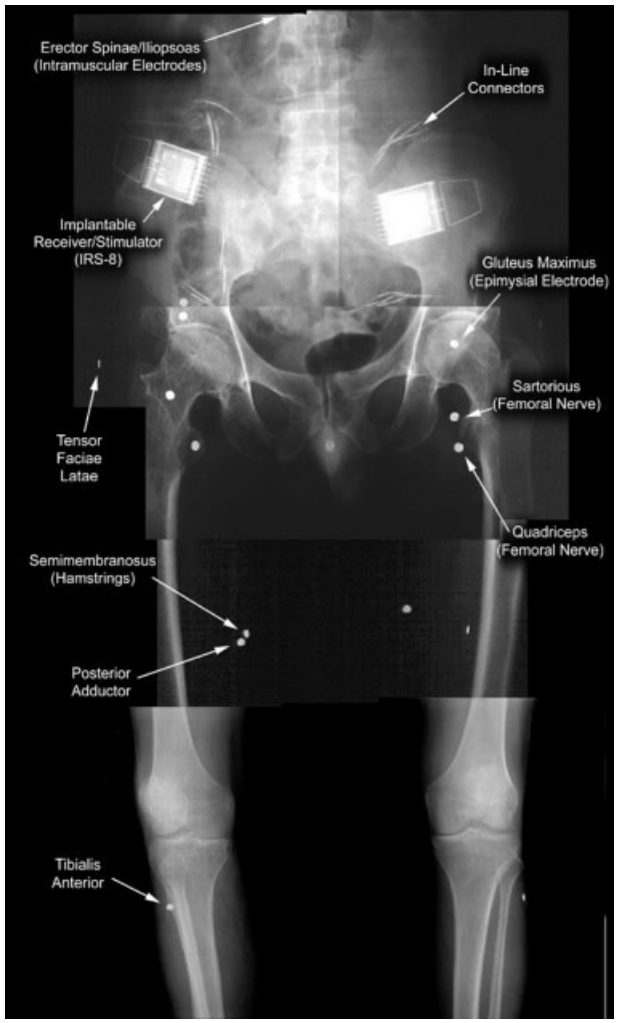

FIGURE 5. A radiograph of a 16-channel implanted lower-limb mobility neuroprosthesis system for paraplegia. (Reproduced with permission. Kobetic et al. IEEE Trans Rehabil Eng 1999;7: 390–398. © 1999 IEEE.)

Stroke. The initial application of neuroprostheses in hemiplegia focused on transcutaneous peroneal nerve stimulation to treat ankle dorsiflexion weakness. In a 1961 publication, Lieberson et al.[187] described a stimulator that dorsiflexes the ankle during the swing phase of gait. In the only randomized study of transcutaneous peroneal stimulation, Burridge et al.[46] reported that stroke survivors treated with the device exhibit significantly greater increase in walking speed with the device relative to baseline without the device, whereas the control group does not. However, despite demonstrated effectiveness, transcutaneous peroneal

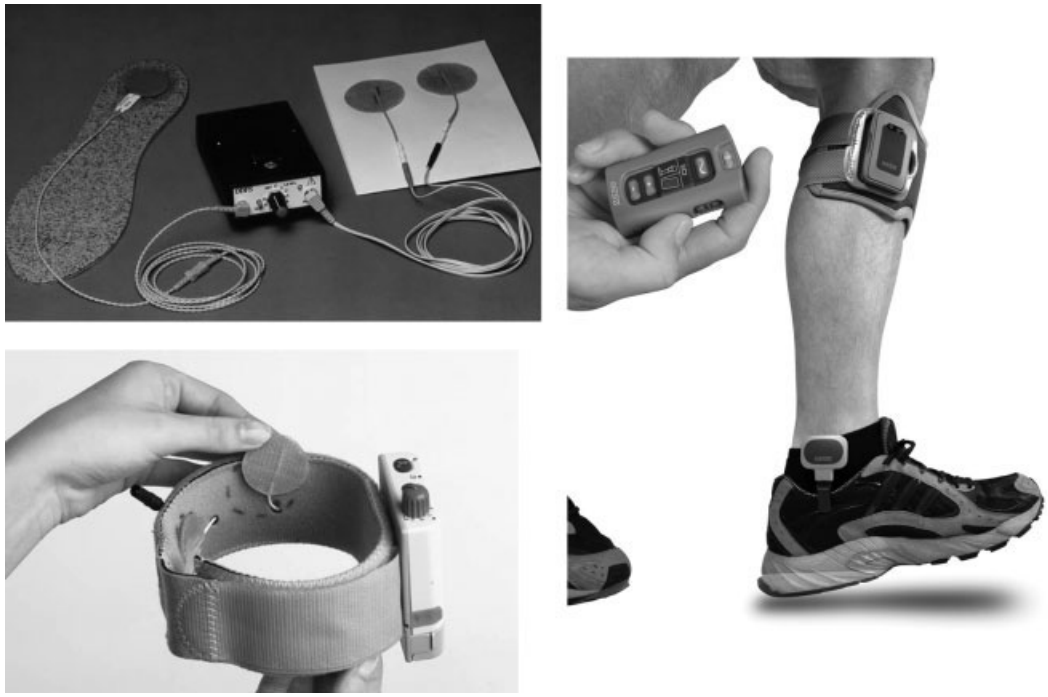

FIGURE 6. Three FDA-approved transcutaneous peroneal nerve stimulators. The Odstock Dropped Foot Stimulator (top left, courtesy of Department of Medical Physics and Biomedical Engineering, Salisbury District Hospital, Salisbury, UK.) and the wireless NESS L300 (right, courtesy of Bioness Inc., Santa Clarita, CA) both use a heel switch to trigger ankle dorsiflexion. The WalkAide (Bottom left, courtesy of Hanger Orthopedic Group/Innovative Neurotronics, Bethesda, MD) uses a tilt sensor to trigger ankle dorsiflexion.

nerve stimulation is not routinely prescribed in the United States for footdrop in hemiplegia. Likely reasons are difficulty with electrode placement, insufficient medial–lateral control during stance phase, lack of technical support, and the availability of custom-molded ankle–foot orthoses. Nevertheless, recent FDA approval of three surface peroneal nerve stimulators (Fig. 6) and demonstrated comparability of the peroneal nerve stimulator to an ankle–foot orthosis in improving hemiplegic gait[252] may facilitate broader clinical prescription and usage of these devices.

Implantable systems may address the difficulties associated with transcutaneous systems. An early study by Waters et al.[299] reported a significant increase in walking speed, stride length, and cadence with a single-channel implantable device relative to preimplantation performance. However, technical limitations include difficulty in balancing inversion and eversion, lack of an in-line connector, which necessitates removal of the entire implant in the event of component failure, and poor reliability of the heel switch and foot-floor contact transmitter. Kljajic et al.[158] also reported significant benefit of a single-channel implantable stimulator. However, nearly half of all subjects require reimplantation due to electrode displacement or failure. At present, two multichannel implantable peroneal nerve stimulators are undergoing clinical investigations in Europe. A dual channel device developed at the University of Twente and Roessingh Research and Development (The Netherlands) stimulates the deep and superficial peroneal nerves for better control of eversion and inversion (Fig. 7).[148] A four-

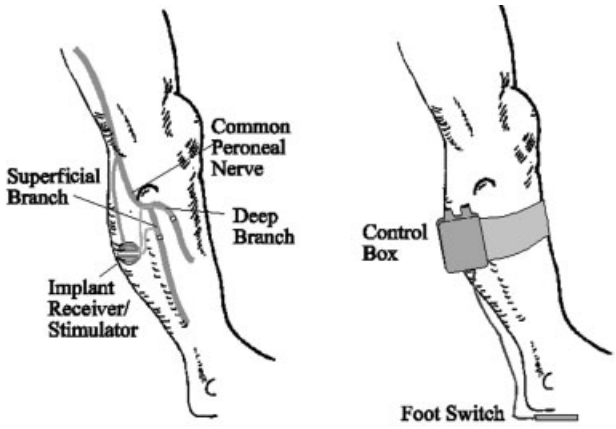

FIGURE 7. A two-channel implantable peroneal nerve stimulator (STIMuSTEP) allows individual stimulation of the deep and superficial branches of the common peroneal nerve for eversion-inversion balance. (Courtesy of Department of Medical Physics and Biomedical Engineering, Salisbury District Hospital, Salisbury, UK.)

channel device, developed at Aalborg University (Denmark) utilizes a nerve cuff with four tripolar electrodes, oriented to activate different nerve fibers within the common peroneal nerve.[44] Both devices have the CE mark in Europe. Finally, an injectable microstimulator, which is percutaneously placed via a minimally invasive procedure, is also under investigation for the correction of foot drop.[303]

In order to address gait deviations due to deficits proximal to the ankle, several studies have evaluated multichannel transcutaneous systems.[29,30,271] However, although these systems were clinically implemented as neuroprostheses, neuroprosthetic outcomes were not assessed. Instead, these studies focused on therapeutic or motor relearning effects and therefore are discussed in the section on motor relearning.

In summary, although the development of lower-limb neuroprostheses for hemiplegia is further along than upper-limb systems, several issues presently limit their clinical implementation. First, transcutaneous systems are limited by discomfort and difficulty with electrode placement for reliable muscle contraction. Percutaneous and implanted systems may address these issues, but potential benefits must be tempered with the risks and costs associated with an invasive procedure. Second, the indications for the level of complexity required for a specific individual remain undefined. Some individuals will require complex multichannel systems, whereas simple dorsiflexion assist devices will suffice for others. Third, it remains unclear as to when the motor relearning period ends and the indication for FES for neuroprosthetic purposes begins. Nearly all studies in this review report some evidence of motor relearning, even among chronic stroke survivors. Finally, clinical relevance must be established by evaluating the effects of the intervention on mobility and quality of life, and by comparing the neuroprosthetic system to a comparable standard of care such as the ankle–foot orthosis. Despite these issues, there are sufficient data to justify pursuit of large, multicenter, randomized clinical trials to demonstrate the clinical efficacy of simple transcutaneous peroneal nerve stimulators for ankle dorsiflexion assist. The development of more sophisticated implanted systems that activate multiple muscles is presently under investigation and should be pursued further.

Bladder Neuroprosthesis. Patients with suprasacral spinal cord lesions can have electrical stimulation applied to the intact sacral nerves or nerve roots to produce effective micturition and improve bowel function,[141] significantly reducing complications and costs of bladder and bowel care.[71] An implantable device for this purpose used by over 2,000 patients in at least 20 countries is presently FDA-approved in the United States and has the CE mark in Europe (Fig. 8).[41,289] Micturition by electrical stimulation requires intact parasympathetic neurons to the detrusor muscle. The function of these neurons is demonstrated by reflex detrusor contractions on a cystometrogram. Patients are implanted at any time after reaching neurologic stability. They should also have an appropriate degree of emotional and social stability. Frequent urinary tract infections and problems tolerating catheters or anticholinergic medication are further indications. Electrodes are placed either intradurally on the sacral anterior nerve roots in the cauda equina via a lower lumbar laminectomy, or extradurally on the mixed sacral nerves in the sacral canal via a laminectomy of S1–3.[72] Intraoperative electrical stimulation and recording of bladder pressure is used to confirm the identity of the nerves supplying the bladder. Leads from the electrodes are tunneled subcutaneously to a radio-receiver/stimulator placed under the skin of the abdomen or chest and powered and controlled by a battery-powered remote control operated by the patient. Posterior rhizotomy is performed to abolish detrusor hyperreflexia and eliminate reflex incontinence. Postoperatively, urodynamic studies are used to guide the setting of stimulus parameters to give an acceptable voiding pressure and rate and pattern of flow. The stimulus program is checked between 1 and 3 months after surgery since the response of the bladder may change with repeated use; thereafter, review is recommended at least annually, monitoring lower and upper urinary tract function.[59]

The majority of patients with an implanted bladder neuroprosthesis use the device routinely for micturition 4–6 times per day. Urodynamic studies show substantial increases in bladder capacity and compliance following posterior rhizotomy.[191,291] Residual volumes in the bladder following implant-driven micturition are usually less than 60 ml and often less than 30 ml.[288,289] The use of the implant is associated with significant reduction in the incidence of symptomatic urinary tract infections.[42,68,193,289] Continence is achieved in over 85% of patients,[92,290] although 10%–15% report some stress incontinence of urine following the procedure.[191] Several centers in Europe have long-term follow-up experience with the device, particularly with regard to the upper tracts.[243,288,289,291] Trabeculation, ureteric reflux, and hydronephrosis tend to decrease in patients who undergo implantation and posterior rhizotomy. There is also a reduction in the incidence of auto-

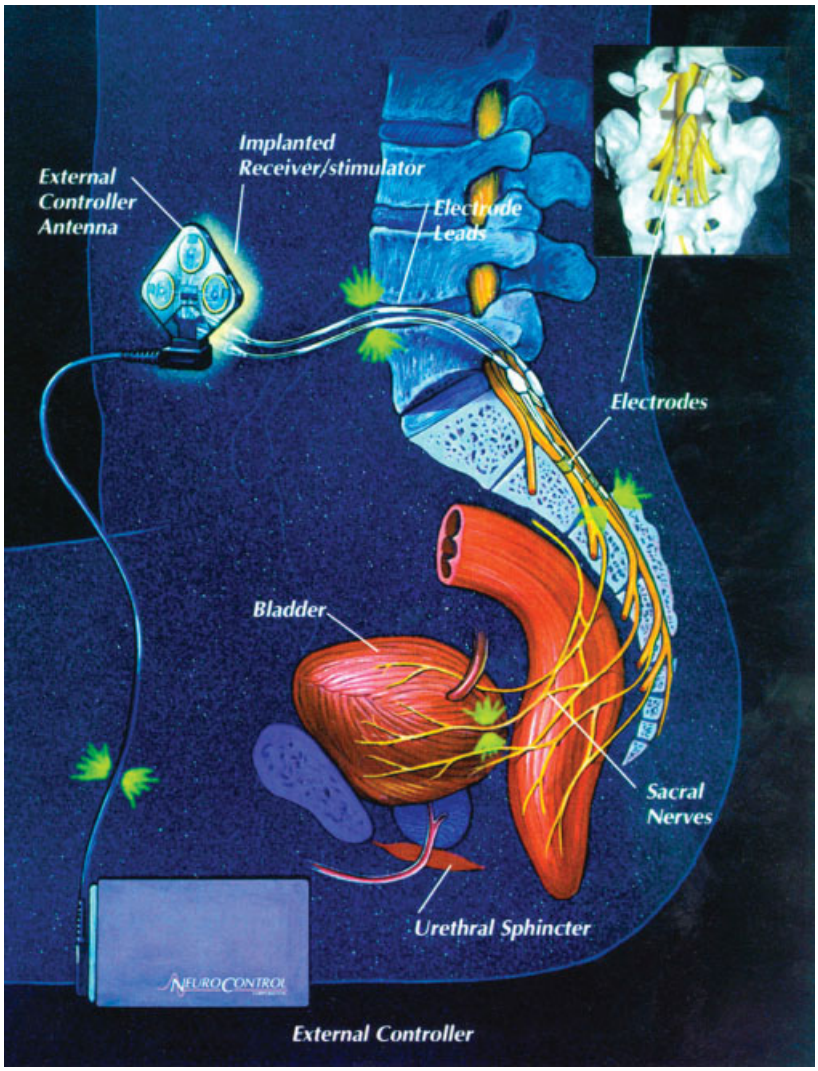

FIGURE 8. The implanted bladder neuroprosthesis system (Vocare, courtesy of NeuroControl, North Ridgeville, OH).

nomic dysreflexia due to the interruption of afferent fibers from the bladder. Reduction of urinary tract infection results in substantial reduction in antibiotic usage. Regular stimulation of the sacral parasympathetic nerves contributes to transport of stool through the distal colon into the rectum, and most users report a reduction in constipation and the need for laxatives and stool softeners.[192] Finally, studies in Europe and the USA indicate that the use of the implanted stimulator together with posterior sacral rhizotomy results in substantial savings in the cost of bladder and bowel care, particularly from reduction in supplies needed for bladder care, medications, and visits to physicians for management of complications.[71,73,304]

Infection of these implants is rare, occurring in 1% of the first 500 implants. Infection is usually introduced at surgery or through a subsequent break in the skin. However, a technique of coating the implants with antibiotics reduces the infection rate.[247] Technical faults in the implanted equipment are uncommon, occurring on average once every 19.6 implant-years.[41] The most common sites for faults are in cables, which are repaired under local anesthesia.

In summary, electrical stimulation of the sacral parasympathetic nerves restores effective micturition for persons with suprasacral spinal cord damage, reducing urinary tract infections and the use of catheters. It is often combined with posterior sacral rhizotomy to increase bladder capacity and abolish reflex incontinence and sphincter contraction. The rhizotomy also reduces the risk of renal damage and autonomic dysreflexia, and the use of anticholinergic medication and urine collection devices; however, it also abolishes reflex erection and reflex ejac-

ulation, which may need to be provided by alternative techniques. Overall, these interventions dramatically improve bladder and bowel function, reduce complications and costs, and increase quality of life after spinal cord injury.

Although the implanted neuroprosthesis is clearly effective in providing urine storage and micturition, the need for a rhizotomy dampens the level of enthusiasm among both clinicians and patients. In order to address this issue, various groups are investigating alternative means of reducing detrusor hyperactivity. Sensory neuromodulation via stimulation of the dorsal penile/clitoral nerve increases bladder capacity among patients with SCI[8] and multiple sclerosis.[249] However, the approach does not abolish reflex sphincter contractions. Thus, other investigators focus on direct blockage of nerve impulses via high-frequency electrical stimulation. Although this approach is still at the level of animal experimentation, its clinical implications reach far beyond the bladder application[24] and may include management of the broader problems of spasticity and pain.[25,151] Other forms of neuromodulation to treat uninhibited bladder contractions are reported in the literature.[241] However, these are generally applied to able-bodied populations and thus are not included in this review.

Respiratory Neuroprostheses. Phrenic nerve pacing has been applied to more than 1,200 patients worldwide and is now a clinically accepted technique to provide artificial ventilatory support in patients with trauma, with respiratory failure secondary to cervical SCI.[108,109,112,136,137,284] There are several commercially available phrenic nerve pacing systems, but each system has a similar configuration. The stimulating electrodes are implanted directly on each phrenic nerve. Small wires tunneled subcutaneously connect the electrodes to an RF receiver, which is implanted in an easily accessible area over the anterior portion of the thorax. External antennas connect to the transmitter. The transmitter generates an RF signal, which is inductively coupled to the implanted receiver. The signal is demodulated by the receivers, which converts it to electrical signals, and then delivered to the stimulating electrodes. Bilateral phrenic nerve stimulation results in descent of each diaphragm and decrease in intrathoracic pressure resulting in inspiration. Cessation of stimulation results in diaphragm relaxation, an increase in intrathoracic pressure, and exhalation.

All potential candidates must demonstrate intact phrenic nerves on nerve conduction studies. They must be free of significant lung disease or primary muscle disease. Patients' psychosocial conditions are also important considerations. Before any technical assessment a critical evaluation of the motivation of both the patient and family members is mandatory. The patient should also have a clear understanding of the potential benefits to be achieved.

Electrodes are positioned around the phrenic nerve in either the cervical region or within the thorax.[108,110,112] Although the thoracic approach requires a thoracotomy, this is the preferred approach, as the cervical approach has the risk of not being able to stimulate the entire nerve.[100,293] An RF receiver is positioned in a subcutaneous pocket on the anterior chest wall. Wires from the electrode are passed through the 3rd or 4th intercostal space and connected to the receiver. Postimplantation, the diaphragm must be gradually reconditioned to improve strength and endurance.[111] During the conditioning phase the patient must be monitored for signs of fatigue, which is usually manifested by the patient's complaint of shortness of breath or reduction in inspired volume.

Although a number of complications have been reported since phrenic nerve pacing was first introduced, technical developments and patient experience have markedly reduced their incidence.[85,107] Nevertheless, all patients require a back-up mechanical ventilator in the event of pacemaker failure. Reported modes of failure include (1) low battery charge, (2) antenna wire breakage, (3) iatrogenic injury to the phrenic nerve, (4) postimplantation adverse tissue reaction and scar tissue formation, (5) device infections, (6) collapse of the upper airway or obstructive apnea due to diaphragm contraction without coincident contraction of the upper airway muscles, and (7) in children, reduction in inspired volume due to paradoxical movement of the rib cage.

Phrenic nerve pacing is clearly an effective means of providing ventilatory support with significant advantages over mechanical ventilation.[108,109,112] Unfortunately, there are few recent analyses of modern-day success rates and incidence of side effects and complications. A long-term follow-up study of 14 tetraplegic patients who use bilateral low-frequency stimulation reported successful use of the device for as long as 15 years, with a mean use of 7.6 years.[107] A more recent study of 64 patients (45 tetraplegic patients) who underwent phrenic nerve pacing for a mean of 2 years showed the incidence of electrode and receiver failure as 3.1% and 5.9%, respectively, which is significantly lower than earlier reports. At this time there are no controlled studies relative to mechanical ventilators. However, it is possible that phrenic nerve pacing improves life expectancy in

patients with tetraplegia. Carter et al.[51] reported only 63% survival at 9 years for patients on positive pressure ventilation. In contrast, all 12 tetraplegic patients who completed the Yale phrenic nerve pacing protocol were alive after 9 years.[93]

Phrenic pacing provides important health and lifestyle benefits relative to mechanical ventilation. However, many patients with ventilator-dependent tetraplegia cannot be offered phrenic nerve pacing due to partial or complete injury of one of the phrenic nerves. Combined intercostal and unilateral diaphragm pacing may be a useful therapeutic modality in selected patients with only unilateral phrenic nerve function.[84] Conventional placement of phrenic nerve electrodes carries the risk of phrenic nerve injury and generally requires a thoracotomy, which is a major surgical procedure with associated risk, in-patient hospital stay, and high cost. Preliminary results suggest that intramuscular diaphragm pacing provide similar benefits as conventional phrenic nerve pacing without the need for an invasive surgical procedure and less risk of phrenic nerve injury.[83] The laparoscopy guided procedure is performed on an outpatient basis and is therefore less costly. The development of fully implantable intramuscular diaphragm system will eliminate the need for the application of devices on the body surface and the risk of decoupling between the transmitter and receiver.

NMES FOR MOTOR RELEARNING

Evolving basic and clinical studies on central motor neuroplasticity support the role of goal-oriented, active repetitive movement training of a paretic limb to enhance motor relearning. Asanuma and Keller[12] demonstrated that electrical stimulation of the somatosensory cortex alone or in conjunction with thalamic stimulation in an animal model induces long-term potentiation (LTP) in the motor cortex. They hypothesized that proprioceptive and cutaneous afferent impulses associated with repetitive movements induce LTP in the motor cortex, which then modify the excitability of specific motor neurons and facilitate motor relearning.[11] Consistent with this hypothesis, nonhuman primate research has demonstrated that after local damage to the motor cortex, goal-oriented, active repetitive movement training of the paretic limb shapes subsequent functional reorganization in the adjacent intact cortex, and that the undamaged motor cortex plays an important role in motor relearning.[214] Specific types of behavioral experiences that induce long-term plasticity in motor maps are repetitive movements that entail the development of new motor skills. That is, the motor tasks are new and therefore "require" significant cognitive effort to complete.[213] When animals are trained to perform new tasks such as retrieving food pellets from a small well[212,215,230] or a rotating well,[157] there is evidence of task-specific cortical reorganization. However, repetitive movement tasks that do not require new skill acquisition (i.e., motor tasks that are already mastered and therefore are easy to carry out and require minimal or no cognitive effort) are not associated with any significant changes in the motor cortex.[157,230]

If goal-oriented, repetitive movement therapy facilitates motor relearning, it is possible that electrical stimulation–mediated goal-oriented repetitive movement therapy also facilitates motor relearning. Acute administration of electrical stimulation to a peripheral nerve activates both sensory and motor structures in the brain[82,270] and reduces intracortical inhibition.[229,239] Functional magnetic resonance imaging (fMRI) studies show activation of the contralateral somatosensory cortex and bilateral supplementary motor areas in response to NMES-mediated wrist extension activity,[120] as well as a dose–response relationship between fMRI and NMES of the lower-limb muscles.[262] These data suggest that repetitive movement therapy mediated by NMES has the potential to facilitate motor relearning via cortical mechanisms.

It is also possible that electrical stimulation facilitates motor relearning via spinal mechanisms. Rushton[246] theorized that the corticospinal–anterior horn cell synapse is a Hebb-type, modifiable synapse and that the synapse can be modified by NMES. "Hebb's rule" proposed in 1949 by Donald Hebb[126] states: "When an axon of cell A. . .excite[s] cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells so that A's efficiency as one of the cells firing B is increased." The synapse is thought to be strengthened by the coincidence of presynaptic and postsynaptic activities. Under normal circumstances neural activity in the pyramidal tract easily discharges the anterior horn cells and the strength of the presumed Hebb-type pyramidal tract/anterior horn cell synapse is maintained by this traffic. However, following brain injury, neural activity in the pyramidal tract is significantly reduced. Failure to restore this traffic leads to "decorrelation" of presynaptic and postsynaptic activities, which weakens the synapse. Rushton suggested that NMES-mediated antidromic impulses provide an artificial means to synchronize presynaptic and postsynaptic activity in the affected population of anterior horn cells. Accord-

ingly, he predicted that combining NMES with simultaneous voluntary effort is an effective means of facilitating motor relearning.

This article limits the review of NMES effectiveness in enhancing motor relearning to the stroke population. Although there is evidence of the role of NMES in facilitating motor relearning in SCI, the breadth and depth of this literature is limited.[199] NMES can be used by patients with hemiparesis who do not have enough residual movement to take part in volitional, active repetitive movement therapy. Regardless of cortical or spinal mechanisms, the experimental and theoretical considerations suggest that the necessary prerequisites for NMES-mediated motor relearning include repetition, novelty of activity, concurrent volitional effort, and high functional content.

Three types of electrical stimulation are available for motor relearning: cyclic NMES, electromyography (EMG)/biofeedback-mediated NMES, and neuroprostheses. Cyclic NMES activates paretic muscles at a set duty cycle for a preset time period. The patient is a passive participant and does not require a cognitive investment, in the form of either initiation of muscle contraction, interpretation of afferent signals, or functionality of motor task. The second type of NMES includes EMG or biofeedback-mediated electrical stimulation, which couples afferent feedback to NMES-induced repetitive movement therapy. These techniques may be applied to patients who can partially activate a paretic muscle but are unable to generate sufficient muscle contraction for adequate exercise or functional purposes. Whereas the patient is a passive participant when using cyclic NMES, EMG or biofeedback-mediated NMES requires greater cognitive investment, which may result in greater therapeutic benefit. The third type of NMES includes neuroprosthetic applications that provide FES. In this strategy repetitive movement training is performed in the context of meaningful, functional behavioral tasks and has a theoretical advantage over both cyclic and EMG/biofeedback mediated NMES.

Upper-Limb Applications. There are four randomized clinical trials investigating the efficacy of cyclic NMES in enhancing upper-limb motor relearning.[56,234,268,269,307] Note that the two studies by Sonde et al.[268] refer to the same study with the 1998 publication reporting end of treatment results and the 2000 publication[269] reporting 3-year follow-up results. All four studies reported improved outcomes in motor impairment at the end of treatment, with mild to moderately impaired subjects benefiting most. Among the three studies that provided follow-up data, the two acute stroke studies reported enduring effects,[56,234] whereas the one chronic study did not.[269] All four studies evaluated activity limitation. However, only two of these reported improvements at the end of treatment,[234,307] and the one study with follow-up data demonstrated no enduring effect on activity limitation.[234]

In the most methodologically sound of the four studies, Powell et al.[234] reported that isometric wrist extension torques were significantly higher for the treatment group at the end of treatment and at 32 weeks. The grasp and grip subscores of the Action Research Arm Test were significantly higher for the treatment group at the end of treatment, but not at 32 weeks. A post-hoc subset analysis indicated that the intervention was most effective for those with residual wrist extension torque at study entry.

The strengths of these studies rest on their randomized designs. However, numerous methodological limitations render the results difficult to interpret. Two of four studies were not blinded.[268,269,307] Of the two blinded studies, only one was double-blinded.[56] Three of four studies reported unequal treatment intensity where the treatment group received NMES and "therapy," while the control group received only "therapy."[234,268,269,307] Of the two studies with follow-up data, the one study with a significant drop-out rate did not use intent-to-treat analysis.[56] Although methodological limitations prevent formulation of definitive conclusions, these four randomized trials do suggest that cyclic NMES enhances the upper-limb motor relearning of stroke survivors. The effect appears to be more significant and enduring for acute stroke survivors and for those with milder baseline impairments. The effect of cyclic NMES on activity limitations, however, remains uncertain.

There are six controlled trials using EMG biofeedback, position, or EMG-triggered NMES for upper-limb motor relearning.[34,54,55,102,156,166] All six studies demonstrated improved outcomes in motor impairment at the end of treatment. In the one study with follow-up data, the effect was enduring after 9 months of follow-up.[166] In the two studies that evaluated activity limitation, improved outcomes were noted.[102,156] Finally, three studies reported evidence of central mechanisms using neurophysiologic assays such as reaction time and fMRI.[54,55,156]

In the most recent of the six studies, Kimberly et al.[156] evaluated 16 chronic stroke survivors in a double-blinded, randomized clinical trial. The treatment group received 60 hours of NMES therapy over a 3-week period applied to the extensor muscles of the hemiplegic forearm to facilitate hand opening. Half

of the 60 hours were devoted to EMG-triggered NMES and the other half to cyclic NMES. The control group received sham treatment, but participants were asked to extend the finger in a repetitive manner. The EMG-triggered NMES group demonstrated significant improvements in measures of grasp and release of objects (box and block test and Jebsen Taylor hand function), isometric finger extension strength, and self-rated activity limitation (motor activity log). In addition, using fMRI and a finger-tracking task, an index of cortical intensity in the ipsilateral somatosensory cortex (relative to hemiparetic limb) increased significantly from pretest to posttest following treatment. The participants receiving sham treatments did not improve on any of the outcome measures except isometric finger extension strength.

Unfortunately, as with the cyclic NMES studies, numerous methodological deficiencies limit the interpretation of results. Only two of six studies[102,156] used blinded assessments. Five of the six studies did not include follow-up evaluations.[34,54,55,102,156] The one study with long-term follow-up did not use a randomized design.[166] Only one study was double-blinded.[156] In all studies, demographic or baseline differences between groups were present or differences could not be assessed. One of the two studies that reported improvements in activity limitation used a modified version of the self-care component of the Functional Independence Measure with unknown psychometric properties.[102] Finally, all studies used small sample sizes. As with cyclic NMES, methodological limitations prevent formulation of definitive conclusions regarding the effectiveness of EMG or biofeedback-mediated NMES. Nevertheless, data suggest that such NMES reduced upper-limb motor impairment and these changes, to at least some degree, translated into improvements in activity limitations.

Finally, hand neuroprostheses may facilitate motor relearning. Studies evaluating hand neuroprostheses for persons with hemiplegia were reviewed earlier.[5,6,58,203,238] Although the primary objective of these earlier studies was to demonstrate a neuroprosthetic effect, nearly all reported some evidence of improved motor ability when the device was turned off. More recent studies used neuroprostheses to specifically demonstrate a motor relearning effect. Alon et al.[7] reported on 77 chronic stroke survivors treated with a home-based training program using the previously described hybrid brace-NMES neuroprosthesis. After 5 weeks of training, significant improvements in motor impairment and activity limitations were noted relative to baseline. In the only controlled trial of an upper-limb neuroprostheses as a motor relearning tool, Popovic et al.[231] reported that performing intensive exercises with the assistance of a neuroprosthesis resulted in significant improvement in upper-limb motor function in acute hemiplegia.

Lower-Limb Applications. A limited number of studies have explored the potential motor relearning effect of NMES in the lower limb. As noted earlier, Lieberson et al.[187] described the first single-channel transcutaneous peroneal nerve stimulator to provide ankle dorsiflexion during the swing phase of gait. However, they also commented that, "On several occasions we observed, after training with the electrophysiologic brace [peroneal nerve stimulator] . . .patients acquire the ability of dorsiflexing the foot by themselves." Since then, numerous case series using either implanted or transcutaneous systems have described similar observations of improved ambulation function, more normal EMG muscle activation patterns, emergence of EMG signals in previously silent muscles, increased strength of EMG activity, and decreased co-contraction of antagonist muscles.[48,158,272,278,279,283,299] The role that voluntary drive plays on motor relearning in repetitive electrical stimulation has been explored.[150] However, to date there are no blinded randomized clinical trials evaluating the motor relearning effects of a peroneal nerve stimulator during ambulation training.

Merletti et al.[204] demonstrated increased dorsiflexion moments in hemiparetic subjects treated with cyclic peroneal nerve stimulation. Studies of stroke patients treated with lower-limb NMES have demonstrated enhanced walking ability, increased maximal isometric contraction of the ankle dorsiflexors and plantarflexors, increased dorsiflexion torque, increased agonist EMG activity, and decreased EMG co-contraction ratios.[184,309] EMG-triggered NMES of the lower limb is associated with increases in voluntary EMG activity and mobility.[99] FES combined with biofeedback is associated with improvements in knee and ankle joint angles, ambulation velocity, symmetry in stance phase, and cycle time.[69] Finally, Burridge et al.[45] reported that after an extended period of use of a transcutaneous peroneal nerve stimulator, a subset of subjects no longer needed the device due to improved ankle control, thought to be secondary to motor relearning.

Since gait deviation in hemiplegia is not limited to ankle dysfunction, several studies have investigated multichannel transcutaneous stimulation systems. Stanic et al.[271] reported significant improve-

ments in qualitative and quantitative measures of gait after training with a 6-channel transcutaneous neuroprosthesis system, which provided ankle dorsiflexion, eversion, and plantarflexion, knee flexion and extension, and hip extension and abduction. Bogataj et al.[30] reported similar findings with a 6-channel NMES system, which provided ankle dorsiflexion and plantarflexion, knee extension and flexion, and hip extension. There was sufficient motor relearning effect to allow all subjects to continue with gait training without the neuroprosthesis. Bogataj et al.[29] also reported a controlled trial of a multichannel transcutaneous neuroprosthesis system for hemiplegic gait. They reported significantly greater improvements in gait performance and motor function among participants treated with the neuroprosthesis for 3 weeks compared with those treated with conventional therapy.

As the number of electrodes increases, transcutaneous systems become more difficult to implement clinically. Reduced muscle selectivity, poor reliability of stimulation, and pain of sensory stimulation further limit the practicality of multichannel transcutaneous lower-limb systems. Accordingly, Daly et al.[76] are investigating a multichannel percutaneous system to facilitate lower-limb motor relearning and mobility. In a single-blinded randomized clinical trial, chronic stroke survivors receiving percutaneous NMES treatments demonstrated significant improvements in gait components and knee flexion coordination relative to controls who did not receive NMES.[75]

Summary and Future Directions. Despite the numerous methodological limitations of controlled trials to date, the weight of the scientific evidence still suggests that NMES-mediated repetitive movement therapy reduces motor impairment in hemiplegia. There is some evidence that the effect is enduring and translates into clinically relevant improvements in hemiparetic arm-specific activity limitation. Although there are theoretical bases for expecting that EMG-triggered NMES is more effective than cyclic NMES, there are no direct comparison studies demonstrating the superiority of one over the other. Similarly, there is limited experimental evidence that neuroprostheses facilitate motor relearning. However, due to the high functional content, neuroprostheses may have enhanced efficacy compared to cyclic or EMG-mediated NMES in facilitating motor relearning.

Future investigations should address issues on two fronts. First, the effect of NMES on motor relearning and impact on clinical outcomes should be confirmed by addressing the methodological limitations of prior studies. Future studies should be large, multicenter, randomized clinical trials, which should be at least single-blinded. Investigators should carefully define the subject population including their stroke characteristics, identify potential confounds, and evaluate immediate and long-term outcomes using valid and reliable outcome measures of motor impairment, energy consumption (such as physiologic cost index and oxygen consumption), activity limitations, and quality of life. These trials should directly compare EMG-triggered NMES, cyclic NMES, and neuroprostheses to identify the most effective paradigm and the populations that will most likely benefit from each approach. The second front for future investigations is refinement of stimulation technique to maximize patient compliance and clinical outcomes. Studies should be carried out in order to determine the optimal dose and prescriptive parameters. In order to increase cognitive investment, systems that require initiation, maintenance, and termination of NMES, such as an EMG-controlled NMES system,[57] should be considered. Future studies should also investigate more sophisticated proxies for cognitive intent such as cortical control.[177] Neuroprostheses that provide clear functional benefit to a broad range of stroke survivors should be developed in order to provide goal-oriented, repetitive movement therapy in the context of functional and meaningful tasks. Finally, basic studies should further investigate mechanisms in order to optimize the treatment paradigm.

HEMIPLEGIC SHOULDER PAIN

Shoulder pain is a common complication following stroke.[292] There are many possible causes of shoulder pain in hemiparesis, including adhesive capsulitis, impingement syndrome, complex regional pain syndrome, brachial plexopathy, spasticity, and subluxation.[21] Figure 9 shows a theoretical framework describing the genesis and maintenance of hemiplegic shoulder pain. The general features of this framework include initial spasticity and weakness leading to mechanical instability and immobility of the glenohumeral joint. These conditions may cause pain directly or they may place the capsule and extracapsular soft tissue at risk for micro- and macrotrauma, which then leads to inflammation, immobility, and pain. In view of the importance of repetitive and functional use of the limb for motor recovery, the immobility exacerbates the state of the already paretic muscles (Fig. 9). The cycle repeats with worsening of the condition. Numerous treatment ap-

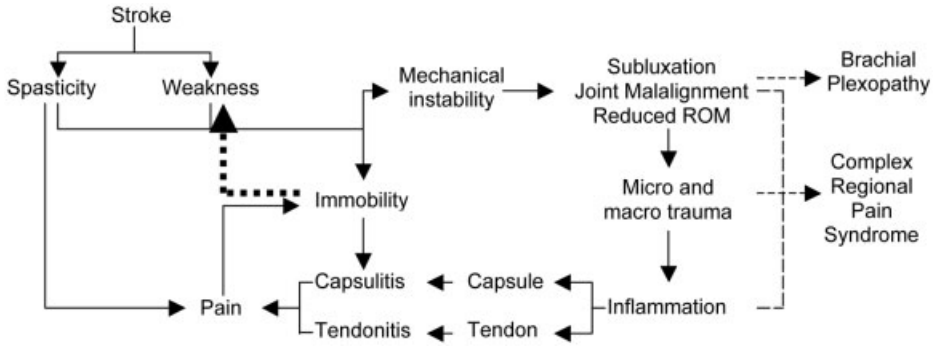

FIGURE 9. Theoretical framework describing the genesis and maintenance of hemiplegic shoulder pain.

proaches have been reported, but with limited success.[263] However, transcutaneous and intramuscular NMES of the supraspinatus, trapezius, and deltoid muscles to reduce subluxation and improve biomechanical integrity and thereby reduce pain are potential treatment options under investigation.

Transcutaneous Systems. There are nine controlled clinical trials of transcutaneous NMES for the treatment of hemiplegic shoulder pain in the literature.[15,61,62,95,161,179,188,297,298] The two publications by Wang et al.[297,298] include separate trials for acute and chronic stroke survivors and the two studies report different outcomes from the same study. Seven studies evaluated NMES as a treatment modality,[15,61,62,161,179,297,298] one evaluated prevention[188] and one evaluated a combination of treatment and prevention.[95] Five studies evaluated acute stroke survivors,[61,62,95,188,297,298] two studies evaluated a combination of acute and chronic stroke survivors,[15,179] and two studies evaluated chronic stroke survivors.[161,297,298]

Radiographic glenohumeral subluxation is the most consistently evaluated outcome measure. Eight of nine studies[15,61,62,95,161,188,297,298] evaluated radiographic inferior glenohumeral subluxation and seven of these[15,61,62,95,161,188,297,298] reported improvements. The six of seven trials that demonstrated a significant effect on subluxation included only acute stroke survivors[61,62,95,188,297] or a combination of acute and chronic stroke survivors.[15] Among these, only two reported sustained improvements beyond the end of treatment.[61,95] A more recent trial of chronic stroke survivors reported no significant effect on inferior subluxation.[297] The one trial of chronic stroke survivors reported significant effect by stressing or loading the hemiparetic upper limb.[161] Without this stressing, there was no significant difference in subluxation between treatment and control groups.

Other commonly evaluated measures include pain-free passive range of motion (ROM), motor impairment using a standardized measure, and resting shoulder pain. Several studies[61,95,179,188,298] evaluated pain-free passive ROM; significant and sustained improvement in pain-free ROM in the treatment group compared to controls was reported in only one study.[61] In two studies[95,179] improvements were noted only using within-group analyses, i.e., the authors reported significant changes in pain-free ROM in the treatment group compared to baseline, but this was not the case in the control group. Three studies reported no significant effect. Several studies evaluated motor impairment using a standardized measure.[61,62,95,188,298] Two acute studies reported improvements at end of treatment and at follow-up.[61,298] One acute study demonstrated improvement at the end of treatment, but not at follow-up.[95] Three studies (two acute and one chronic) reported no improvements in motor impairment.[62,188,298] Two treatment and one prevention studies evaluated shoulder pain at rest. The treatment studies reported improvements, whereas the prevention study did not.

As with NMES for motor relearning, numerous methodological limitations make these results difficult to interpret. Seven of the nine studies used small sample sizes.[62,95,161,179,188,297,298] Only three studies were blinded.[15,179,188] Of these, only one study was double-blinded,[179] but the sample size was too small to make any definitive statistically statement.

Two meta-analyses of the efficacy of NMES for the treatment of hemiplegic shoulder pain have been reported. The Cochrane review[235] assessed four studies[95,179,188,268] and concluded that NMES improved pain-free passive ROM and reduced subluxation, but did not improve shoulder pain or motor impairment. Ada and Foongchomcheay[2] included seven studies[15,95,161,188,297,298] to assess the

effects of NMES on shoulder subluxation and motor impairment as a function of stroke acuity. They concluded that NMES reduced or prevented subluxation and improved motor impairment in the acute phase, but not in the chronic phase. They also concluded that NMES did not improve passive lateral pain-free ROM in the acute phase, but that it may improve active pain-free ROM in the chronic phase. The differences in conclusions between the two meta-analyses are likely due to the differences in inclusion criteria used to accept specific studies in the respective studies.

Intramuscular Systems. Despite the evidence for therapeutic benefit, the clinical use of transcutaneous NMES for shoulder subluxation and pain in hemiplegia is limited for several reasons. First, stimulation of cutaneous pain receptors cannot be avoided, resulting in stimulation-induced pain that limits tolerance and compliance. Second, activation of deep muscles cannot be achieved without stimulation of more superficial muscles. Third, stimulated muscle contraction cannot be titrated precisely. Finally, clinical skill is required to place electrodes and adjust stimulation parameters to provide optimal and tolerable treatment. A potential solution is intramuscular NMES systems, which can be injected or percutaneously placed into the target muscle. These systems are less painful during stimulation, which enhances patient compliance. Motor points do not need to be located with each treatment session, which eases donning and doffing of the device. Since the electrodes are implanted, repeatability and reliability of stimulation are enhanced, which minimizes the need for skilled care. And finally, due to the focal nature and reliability of intramuscular stimulation, the best muscles to stimulate can be identified and current intensity on multiple channels can be titrated easily. Two intramuscular electrical stimulation systems are under investigation: an injectable system with an external antenna and a percutaneous system with an external stimulator.

The previously described injectable microstimulator is presently under investigation to treat hemiplegic shoulder dysfunction. Preliminary results from a randomized clinical trial demonstrated reduction in shoulder subluxation and an increase in the thickness of the stimulated muscles.[88] However, the effect on shoulder pain is still under investigation. The stimulators are permanently implanted and, if shoulder subluxation or pain recurs, additional treatments can be provided without an additional invasive procedure. However, the system also requires a large antenna that must be worn, which may interfere with daily activities and compromise clinical acceptance.

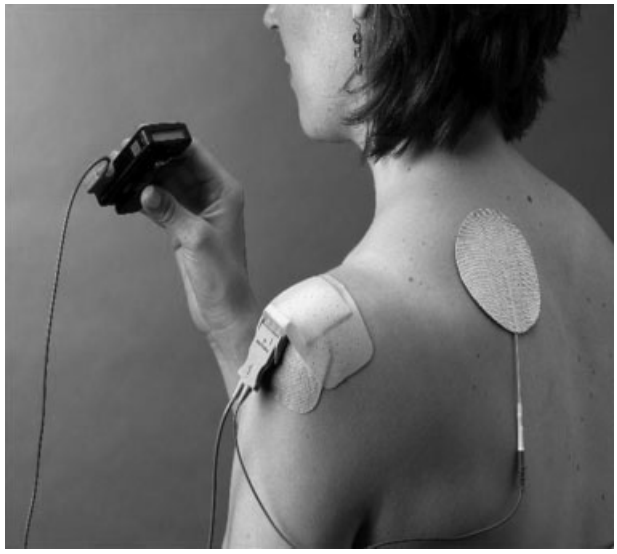

FIGURE 10. A percutaneous intramuscular electrical stimulation system for treatment of hemiplegic shoulder pain. The pager-size stimulator is connected to the implanted electrodes via a connector that can be disconnected when not in use. (RestoreStIM, courtesy of NeuroControl, North Ridgeville, OH.)

The percutaneous system includes helical intramuscular electrodes, which are percutaneous-placed, a "pager" size stimulator, which is worn on a belt, and a connector, which connects the electrodes to the stimulator (Fig. 10). Electrodes traverse the skin and remain across the skin for the duration of treatment. Therefore, the system is at risk for infection. The electrodes are removed by gentle traction after completion of treatment. A multicenter clinical trial demonstrated that the percutaneous system is effective in reducing hemiplegic shoulder pain and improving shoulder pain-related quality of life of chronic stroke survivors for up to 12 months after completion of treatment (Fig. 11).[60,311] There were no instances of electrode-related infections.

Summary. The use of transcutaneous NMES appears to reduce shoulder subluxation and pain-free ROM and facilitate motor recovery, especially among acute stroke survivors. However, additional studies that address the previously noted methodological limitations are needed to address more definitively the question of clinical efficacy. Intramuscular systems are still under investigation. The injectable system is undergoing clinical trials of initial effectiveness for hemiplegic shoulder pain and the percutaneous system is presently being compared to transcutaneous electrical nerve stimulation

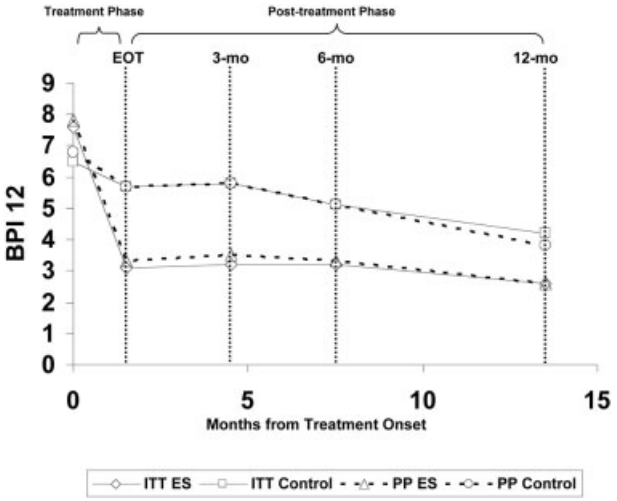

FIGURE 11. Results of multicenter randomized clinical trial of percutaneous intramuscular electrical stimulation (ES) for the treatment of hemiplegic shoulder pain. Per-protocol (PP, dashed lines) and intent-to-treat (ITT, solid lines) approaches both showed that percutaneous intramuscular ES significantly reduces hemiplegic shoulder pain (Brief Pain Inventory Question 12) for up to 12 months after completion of treatment compared with controls who were treated with a cuffed hemisling. (Reproduced with permission, Chae et al. Am J Phys Med Rehabil 2005;84:832–842. © 2005 Lippincott Williams & Wilkins.)

(TENS) in a second clinical trial to satisfy FDA 510K regulatory requirements.

OTHER THERAPEUTIC APPLICATIONS

Muscle Strengthening and Atrophy. Muscle fiber alterations at the cellular level form the basis of the present understanding of NMES-associated muscle strength enhancement. NMES has the ability to reverse the transformation of type I fibers to type II fibers seen in UMN injury.[225,227] The specific effect of NMES-facilitated exercise on the motor unit has been reviewed.[91] Numerous skeletal-muscle biochemical and physiological adaptations are induced by chronic low-frequency electrical stimulation in an animal model.[189] Fast to slow twitch alterations of muscle fibers are associated with alterations of calcium dynamics and myofibrillar proteins; white to red fiber transformations are associated with changes in mitochondrial enzymes, myoglobin, and the induction of angiogenesis.[189] Metabolic and phenotypic characteristics of human skeletal muscle fibers are used as predictors of glycogen utilization during electrical stimulation.[117] Intracellular changes induced by NMES form the basis of muscle strength alterations and preservation in neurological rehabilitation.

In humans, there are physiologic differences between volitional muscle contraction and electrically activated muscle contractions.[81] Human[198] and animal[89] studies characterize how the specific pattern of electrical stimulation impacts muscle strength alterations. A study evaluating healthy men showed that shorter duty cycles produced more fatigue, possibly due to greater intracellular acidosis and reduced availability of high-energy phosphate.[198] Mathematical muscle modeling is proposed to predict the force necessary to achieve therapeutic loading conditions in SCI in order to better define the use of electrical stimulation for isometric training and functional activities.[103] A recent study evaluated the therapeutic effect of combining volitional muscle contraction and electrical stimulation in a training program with healthy adults and did not demonstrate significant benefit from superimposed therapies.[220] Theoretically, a greater number of motor units is recruited with volitional muscle contraction and electrical stimulation as compared to volitional contraction alone due to the phenomenon of reverse recruitment order. However, there is also the theoretical possibility of collision blocking, reducing the net efferent output of the alpha motoneuron.

The literature supports the therapeutic application of NMES to enhance muscle strength, retard muscle atrophy, and reduce spasticity.[16,87] Enhanced quadriceps muscle performance as reflected in load resistance, repetitions, and knee ROM can occur with a NMES knee-extension system used in SCI.[244] Arm crank ergometry with NMES enhances upper-limb manual muscle scores in cervical spinal cord injury.[47] FES cycle ergometry (FES-CE) may provide greater benefit than unloaded isometric FES contractions (FES-IC). A study involving 26 acute SCI subjects demonstrated that an FES-CE training program, but not an FES-IC training program, prevented muscle atrophy at 3 months and caused significant hypertrophy at 6 months.[17] Researchers utilize various methods to quantify morphologic and therapeutic response to NMES including MRI,[216] PET scan,[294] and 99mTC-sestamibi muscle scintigraphy.[226] Although this review confines itself to the role of NMES for persons with SCI and stroke, the ability of NMES to enhance muscle strength and mass for the broader neurologic and orthopedic applications are also reported in the literature.[119,121,174,185,274]

Deep Venous Thrombosis Prevention. NMES may be effective in reducing the risk of venous stasis and thromboembolism. Several studies evaluated NMES for the prevention of neurosurgical postoperative

thromboembolism[32] and post-arthroplasty venous complications including DVT.[208] Cardiovascular effects, consistent with decreased lower-limb venous stasis, including increased stroke volume and cardiac output have been documented when lower-limb electrical stimulation is used during surgery.[96] A study of immobilized subjects showed that electrical stimulation of the foot and calf decreases venous stasis and reduces the risk of DVT.[147] A review article of the etiology, incidence, and prevention of DVT in acute SCI supported the use of electrical stimulation in combination with low-dose heparin for the prevention of thromboembolic disease.[205]

Bone Mass/Density. Physiological alterations of bone associated with immobility in the neurologically impaired patient are well documented. Following SCI, weight-bearing trabecular-rich sites such as the distal femur and proximal tibia show the greatest demineralization. Pathological fractures following minor trauma are caused by reduced bone mass in association with modified bone matrix composition.[194] Animal studies demonstrate the prevention and reversal of osteoporosis with capacitively coupled electrical fields.[37–40,186] Various forms of electrical stimulation affect growth, repair, and remodeling of soft and hard tissues in animals.[28]

Several studies have described the effect of FES lower-limb cycling on bone density in SCI. A trend toward increased bone lumbar spine bone density is seen in chronic SCI with neurogenic osteoporosis.[19] In two studies, FES cycling exercises for 6 months enhanced the bone mineral density of the distal femur and proximal tibia,[20,63] although the effect was not sustained with discontinuance of FES.[63] However, other studies have failed to corroborate these findings.[94,181] A recent review article suggested that FES cycle ergometry helps prevent bone loss in women, specifically with acute spinal cord injuries.[219]

Tissue Oxygenation and Peripheral Hemodynamic Functioning. NMES may improve tissue oxygenation and peripheral hemodynamic function. Eight weeks of stimulation is associated with an increase in the unloaded tissue oxygen level and a reduction in the ischial region pressure, although total interface pressures does not change.[31] Animal studies demonstrate increased microvascular perfusion with transcutaneous NMES.[65–67] The ability of TENS to impact peripheral vascular resistance and cause a transient local increase in blood flow is dependent on stimulation intensity.[253]

The impact of NMES on peripheral hemodynamic functioning is the focus of several studies.[18,52,228,250,313] In one study there was a linear increase in femoral arterial blood flow with increasing stimulation rates of TENS.[313] However, a recent study evaluating peripheral vascular responses to NMES in chronic SCI showed improved muscle fiber size and fatigue without impact on femoral arterial diameter or blood flow.[250] After NMES-assisted treadmill training for 3 months in chronic SCI, there was an increase in systolic blood pressure at rest as well as during exercise.[52] In a study using arm crack ergometry and NMES-induced leg contractions, an increase in blood flow and decrease in venous pooling were associated with a reduced rate pressure product.[228]

Cardiorespiratory Conditioning. Enhancement of cardiorespiratory fitness is associated with the use of NMES in SCI. Exercise recommendations for SCI presently include the use of NMES to facilitate exercise either via NMES leg cycle ergometry or NMES-assisted treadmill gait training.[138] A study of peak and submaximal physiological responses in SCI showed a significant increase in peak rate of oxygen consumption.[135] NMES leg cycle ergometry increases functional capacity in SCI subjects,[70] although high peak NMES-assisted pedal forces contribute to low efficiency in paraplegic subjects.[258] The rate of fatigue during NMES-assisted exercise is greater than during volitional exercise.[27]

NMES-assisted ambulation training and arm ergometry in SCI is associated with central cardiovascular adaptations including increased time to fatigue, peak power output, and peak rate of oxygen consumption.[139] Studies evaluating energy expenditure with NMES-assisted treadmill gait training and partial body-weight support in SCI have shown improvements in the rate of oxygen and energy consumption, which is consistent with enhanced metabolic and cardiovascular responses.[53,79,80]

CONCLUSIONS

The principal goal of rehabilitation management of persons with UMN paralysis is to maximize quality of life. NMES systems bypass the injured central circuitry to activate neural tissue and contract muscles to provide function to what is otherwise a nonfunctioning limb or structure. Recent advances in clinical medicine and biomedical engineering make the clinical implementation of NMES systems to enhance the mobility and function of paralyzed person more feasible. Hand neuroprosthesis systems can

significantly enhance the upper-limb function of persons with tetraplegia. The application of this technology for persons with hemiplegia is in its infancy and must await further technical and scientific developments if it is to be applicable to the broader stroke population. Several lower-limb systems with and without bracing are being investigated for the purpose of functional transfers and standing, and to a lesser degree for ambulation for patients with paraplegia. While multichannel neuroprosthesis systems for hemiplegia are still under development, the footdrop stimulator is ready for large-scale multicenter clinical trials. The bladder neuroprosthesis can provide catheter-free micturition for persons with either paraplegia or tetraplegia. Phrenic and diaphragmatic pacing systems can provide artificial ventilatory support for patients with ventilator-dependent tetraplegia. NMES for motor relearning in hemiplegia is a promising application of goal-oriented repetitive movement therapy and is ready for large-scale multicenter clinical trials. NMES for treatment of shoulder subluxation and pain in hemiplegia has yielded encouraging results and is ready for confirmatory large-scale multicenter clinical trials. Finally, NMES may be effective in strengthening muscles, preventing muscle atrophy, preventing DVT, improving tissue oxygenation and peripheral hemodynamic functioning, and facilitating cardiopulmonary conditioning.

Although this review was limited to applications in the SCI and stroke populations, work with multiple sclerosis,[282] traumatic brain injury,[217] and cerebral palsy[129,218,233] is in its early stages and will undoubtedly expand. Clinical practice is rarely limited to a single intervention. Thus, with the development of pharmacological interventions,[113] neuronal regeneration,[36] and other innovations such as robotic therapy,[97,170] mental imagery,[1] virtual reality,[167,245] and constraint-induced therapy,[281,305] the future will likely embrace combination therapies to treat the motor dysfunction of persons with central nervous system paralysis.

After decades of development, the clinical utility of NMES systems is finally becoming realized. By necessity, scientists and clinicians must continue to explore new ideas and improve upon the present systems. Components will be smaller, more durable, and more reliable. The issues of cosmesis and ease of donning and doffing will require systems to be fully implantable. Control issues will remain central, and the implementation of cortical control will dictate the nature of future generations of neuroprosthesis systems. Future developments will be directed by consumers. In the present healthcare environment where cost is an overwhelming factor in the development and implementation of new technology, the consumer will become one of technology's greatest advocates. Finally, the usual drive toward greater complexity will be tempered by the practical issues of clinical implementation where patient and clinician acceptances are often a function of a tenuous balance between the "burden and cost" associated with using a system and the system's impact on the user's quality of life.

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REFERENCES

1. Abbruzzese G, Assini A, Buccolieri A, Marchese R, Trompetto C. Changes of intracortical inhibition during motor imagery in human subjects. Neurosci Lett 1999;263: 113–116.
2. Ada L, Foongchomcheay A. Efficacy of electrical stimulation in preventing or reducing subluxation of the shoulder after stroke: a meta-analysis. Aust J Physiother 2002;48:257–267.
3. Adrian E. The physical background of perception. Oxford: Clarendon Press; 1946.
4. Agnew WF, McCreery DB. Considerations for safety with chronically implanted nerve electrodes. Epilepsia 1990; 31(Suppl 2):S27–32.
5. Alon G, Dar A, Katz-Behiri D, Wingarden H, Nathan R. Efficacy of a hybrid upper limb neuromuscular electrical stimulation system in lessening selected impairments and dysfunctions consequent to cerebral damage. J Neurol Rehabil 1998;2:73–80.
6. Alon G, McBride K, Ring H. Improving selected hand functions using a noninvasive neuroprosthesis in persons with chronic stroke. J Stroke Cerebrovasc Dis 2002;11:99–106.
7. Alon G, Sunnerhagen KS, Geurts AC, Ohry A. A home-based, self-administered stimulation program to improve selected hand functions of chronic stroke. Neurorehabilitation 2003;18:215–225.
8. Amarenco G, Ismael SS, Even-Schneider A, Raibaut P, Demaille-Wlodyka S, Parratte B, et al. Urodynamic effect of acute transcutaneous posterior tibial nerve stimulation in overactive bladder. J Urol 2003;169:2210–2215.
9. Arbuthnott ER, Boyd IA, Kalu KU. Ultrastructural dimensions of myelinated peripheral nerve fibres in the cat and their relation to conduction velocity. J Physiol (Lond) 1980; 308:125–157.
10. Arcos I, Davis R, Fey K, Mishler D, Sanderson D, Tanacs C, et al. Second-generation microstimulator. Artif Organs 2002; 26:228–231.
11. Asanuma H, Keller A. Neurobiological basis of motor relearning and memory. Conc Neurosci 1991;2:1–30.
12. Asanuma H, Keller A. Neuronal mechanisms of motor learning in animals. Neuroreport 1991;2:217–224.
13. Bajd T, Kralj A, Stefancic M, Lavrac N. Use of functional electrical stimulation in the lower extremities of incomplete spinal cord injured patients. Artif Organs 1999;23:403–409.
14. Bajd T, Kralj A, Turk R. Standing up of a healthy subject and a paraplegic patient. J Biomech 1982;15:1–10.
15. Baker LL, Parker K. Neuromuscular electrical stimulation of the muscles surrounding the shoulder. Phys Ther 1986;66: 1930–1937.
16. Baker LL, Parker K, Sanderson D. Neuromuscular electrical stimulation for the head-injured patient. Phys Ther 1983;63: 1967–1974.

17. Baldi JC, Jackson RD, Moraille R, Mysiw WJ. Muscle atrophy is prevented in patients with acute spinal cord injury using functional electrical stimulation. Spinal Cord 1998;36:463–469.
18. Balogun JA, Biasci S, Han L. The effects of acupuncture, electroneedling and transcutaneous electrical stimulation therapies on peripheral haemodynamic functioning. Disabil Rehabil 1998;20:41–48.
19. BeDell KK, Scremin AM, Perell KL, Kunkel CF. Effects of functional electrical stimulation-induced lower extremity cycling on bone density of spinal cord-injured patients. Am J Phys Med Rehabil 1996;75:29–34.
20. Belanger M, Stein RB, Wheeler GD, Gordon T, Leduc B. Electrical stimulation: can it increase muscle strength and reverse osteopenia in spinal cord injured individuals? Arch Phys Med Rehabil 2000;81:1090–1098.
21. Bender L, McKenna K. Hemiplegic shoulder pain: defining the problem and its management. Disabil Rehabil 2001;23: 698–705.
22. Benton LA, Baker LL, Bowman BR, Waters RL. Functional electrical stimulation: a practical clinical guide. Downey, CA: Ranchos Los Amigos Medical Center; 1981.
23. Betz RR, Mulcahey MJ, Smith BT, Triolo RJ, Weiss AA, Moynahan M, et al. Bipolar latissimus dorsi transposition and functional neuromuscular stimulation to restore elbow flexion in an individual with C4 quadriplegia and C5 denervation. J Am Paraplegia Soc 1992;15:220–228.
24. Bhadra N, Bhadra N, Kilgore K, Gustafson KJ. High frequency electrical conduction block of the pudendal nerve. J Neural Eng 2006;3:180–187.
25. Bhadra N, Kilgore KL. High-frequency electrical conduction block of mammalian peripheral motor nerve. Muscle Nerve 2005;32:782–790.
26. Bigland-Ritchie B, Jones DA, Woods JJ. Excitation frequency and muscle fatigue: electrical responses during human voluntary and stimulated contractions. Exp Neurol 1979;64: 414–427.
27. Binder-Macleod SA, Snyder-Mackler L. Muscle fatigue: clinical implications for fatigue assessment and neuromuscular electrical stimulation. Phys Ther 1993;73:902–910.
28. Black J. Electrical stimulation of hard and soft tissues in animal models. Clin Plast Surg 1985;12:243–257.
29. Bogataj U, Gros N, Kljajic M, Acimovic R, Malezic M. The rehabilitation of gait in patients with hemiplegia: a comparison between conventional therapy and multichannel functional electrical stimulation therapy. Phys Ther 1995;75: 490–502.
30. Bogataj U, Gros N, Malezic M, Kelih B, Kljajic M, Acimovic R. Restoration of gait during two to three weeks of therapy with multichannel electrical stimulation. Phys Ther 1989;69:319–327.
31. Bogie KM, Triolo RJ. Effects of regular use of neuromuscular electrical stimulation on tissue health. J Rehabil Res Dev 2003;40:469–475.
32. Bostrom S, Holmgren E, Jonsson O, Lindberg S, Lindstrom B, Winso I, et al. Post-operative thromboembolism in neurosurgery. A study on the prophylactic effect of calf muscle stimulation plus dextran compared to low-dose heparin. Acta Neurochir (Wien) 1986;80:83–89.
33. Bowman BR, Erickson RC 2nd. Acute and chronic implantation of coiled wire intraneural electrodes during cyclical electrical stimulation. Ann Biomed Eng 1985;13:75–93.
34. Bowman R, Baker L, Waters R. Positional feedback and electrical stimulation: An automated treatment for hemiplegic wrist. Arch Phys Med Rehabil 1979;60:497–502.
35. Bozzo C, Spolaore B, Toniolo L, Stevens L, Bastide B, Cieniewski-Bernard C, et al. Nerve influence on myosin light chain phosphorylation in slow and fast skeletal muscles. FEBS J 2005;272:5771–5785.
36. Bradbury EJ, McMahon SB. Spinal cord repair strategies: why do they work? Nat Rev Neurosci 2006;7:644–653.
37. Brighton CT, Katz MJ, Goll SR, Nichols CE 3rd, Pollack SR. Prevention and treatment of sciatic denervation disuse osteoporosis in the rat tibia with capacitively coupled electrical stimulation. Bone 1985;6:87–97.
38. Brighton CT, Luessenhop CP, Pollack SR, Steinberg DR, Petrik ME, Kaplan FS. Treatment of castration-induced osteoporosis by a capacitively coupled electrical signal in rat vertebrae. J Bone Joint Surg Am 1989;71:228–236.
39. Brighton CT, Tadduni GT, Goll SR, Pollack SR. Treatment of denervation/disuse osteoporosis in the rat with a capacitively coupled electrical signal: effects on bone formation and bone resorption. J Orthop Res 1988;6:676–684.
40. Brighton CT, Tadduni GT, Pollack SR. Treatment of sciatic denervation disuse osteoporosis in the rat tibia with capacitively coupled electrical stimulation. Dose response and duty cycle. J Bone Joint Surg Am 1985;67:1022–1028.
41. Brindley GS. The first 500 patients with sacral anterior root stimulator implants: general description. Paraplegia 1994; 32:795–805.
42. Brindley GS, Polkey CE, Rushton DN, Cardozo L. Sacral anterior root stimulators for bladder control in paraplegia: the first 50 cases. J Neurol Neurosurg Psychiatry 1986;49: 1104–1114.
43. Bryden AM, Memberg WD, Crago PE. Electrically stimulated elbow extension in persons with C5/C6 tetraplegia: a functional and physiological evaluation. Arch Phys Med Rehabil 2000;81:80–88.
44. Burridge J, Haugland M, Larsen B, RM P, Svaneborg, N, Iversen HK, et al. A phase II study to evaluate the safety and effectiveness of the ActiGait implanted drop-foot stimulator in established hemiplegia. J Rehabil Med (in press).
45. Burridge J, Taylor P, Hagan S, Swain I. Experience of clinical use of the Odstock dropped foot stimulator. Artif Organs 1997;21:254–260.
46. Burridge JH, Taylor PN, Hagan SA, Wood DE, Swain ID. The effects of common peroneal stimulation on the effort and speed of walking: a randomized controlled trial with chronic hemiplegic patients. Clin Rehabil 1997;11:201–210.
47. Cameron T, Broton JG, Needham-Shropshire B, Klose KJ. An upper body exercise system incorporating resistive exercise and neuromuscular electrical stimulation (NMS). J Spinal Cord Med 1998;21:1–6.
48. Carnstam B, Larsson LE, Prevec TS. Improvement in gait following electrical stimulation. Scand J Rehabil Med 1977; 9:7–13.
49. Carpaneto J, Micera S, Zaccone F, Vecchi F, Dario P. A sensorized thumb for force closed-loop control of hand neuroprostheses. IEEE Trans Neural Syst Rehabil Eng 2003; 11:346–353.
50. Carraro U, Rossini K, Mayr W, Kern H. Muscle fiber regeneration in human permanent lower motoneuron denervation: relevance to safety and effectiveness of FES-training, which induces muscle recovery in SCI subjects. Artif Organs 2005;29:187–191.
51. Carter RE, Donovan WH, Halstead L, Wilkerson MA. Comparative study of electrophrenic nerve stimulation and mechanical ventilatory support in traumatic spinal cord injury. Paraplegia 1987;25:86–91.
52. Carvalho DC, Cliquet A Jr. Response of the arterial blood pressure of quadriplegic patients to treadmill gait training. Braz J Med Biol Res 2005;38:1367–1373.
53. Carvalho DC, de Cassia Zanchetta M, Sereni JM, Cliquet A. Metabolic and cardiorespiratory responses of tetraplegic subjects during treadmill walking using neuromuscular electrical stimulation and partial body weight support. Spinal Cord 2005;43:400–405.
54. Cauraugh J, Light K, Kim S, Thigpen M, Behrman A. Chronic motor dysfunction after stroke: recovering wrist and finger extension by electromyography-triggered neuromuscular stimulation. Stroke 2000;31:1360–1364.
55. Cauraugh JH, Kim S. Two coupled motor recovery protocols are better than one: electromyogram-triggered neuromuscu-

lar electrical stimulation and bilateral movements. Stroke 2002;33:1589–1594.
56. Chae J, Bethoux F, Bohinc T, Dobos L, Davis T, Friedl A. Neuromuscular stimulation for upper extremity motor and functional recovery in acute hemiplegia. Stroke 1998;29: 975–979.
57. Chae J, Fang ZP, Walker M, Pourmehdi S. Intramuscular electromyographically controlled neuromuscular electrical stimulation for upper limb recovery in chronic hemiplegia. Am J Phys Med Rehabil 2001;80:935–941.
58. Chae J, Hart R. Intramuscular hand neuroprosthesis for chronic stroke survivors. Neurorehabil Neural Repair 2003; 17:109–117.
59. Chae J, Triolo R, Kilgore K, Creasey G, DiMarco AF. Functional neuromuscular stimulation. In: DeLisa J, Gans B, editors. Physical medicine and rehabilitation: principles and practices, Vol. 2. Philadelphia: Lippincott Williams & Wilkins; 2005. p 1405–1426.
60. Chae J, Yu DT, Walker ME, Kirsteins A, Elovic EP, Flanagan SR, et al. Intramuscular electrical stimulation for hemiplegic shoulder pain: a 12-month follow-up of a multiple-center, randomized clinical trial. Am J Phys Med Rehabil 2005;84: 832–842.
61. Chantraine A, Baribeault A, Uebelhart D, Gremion G. Shoulder pain and dysfunction in hemiplegia: effects of functional electrical stimulation. Arch Phys Med Rehabil 1999;80:328–331.
62. Chen CH, Chen TW, Weng MC, Wang WT, Wang YL, Huang MH. The effect of electroacupuncture on shoulder subluxation for stroke patients. Kaohsiung J Med Sci 2000;16:525–532.
63. Chen SC, Lai CH, Chan WP, Huang MH, Tsai HW, Chen JJ. Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. Disabil Rehabil 2005;27:1337–1341.
64. Chen YL, Li YC, Kuo TS, Lai JS. The development of a closed-loop controlled functional electrical stimulation (FES) in gait training. J Med Eng Technol 2001;25:41–48.
65. Clemente FR, Barron KW. The influence of muscle contraction on the degree of microvascular perfusion in rat skeletal muscle following transcutaneous neuromuscular electrical stimulation. J Orthop Sports Phys Ther 1993;18:488–496.
66. Clemente FR, Barron KW. Transcutaneous neuromuscular electrical stimulation effect on the degree of microvascular perfusion in autonomically denervated rat skeletal muscle. Arch Phys Med Rehabil 1996;77:155–160.
67. Clemente FR, Matulionis DH, Barron KW, Currier DP. Effect of motor neuromuscular electrical stimulation on microvascular perfusion of stimulated rat skeletal muscle. Phys Ther 1991;71:397–404.
68. Colombel P, Egon G. [Electrostimulation of the anterior sacral nerve roots]. Ann Urol Paris 1991;25:48–52.
69. Cozean CD, Pease WS, Hubbell SL. Biofeedback and functional electric stimulation in stroke rehabilitation. Arch Phys Med Rehabil 1988;69:401–405.
70. Crameri RM, Weston A, Climstein M, Davis GM, Sutton JR. Effects of electrical stimulation-induced leg training on skeletal muscle adaptability in spinal cord injury. Scand J Med Sci Sports 2002;12:316–322.
71. Creasey GH, Dahlberg JE. Economic consequences of an implanted neuroprosthesis for bladder and bowel management. Arch Phys Med Rehabil 2001;82:1520–1525.
72. Creasey GH, Grill JH, Korsten M, U HS, Betz R, Anderson R, et al. An implantable neuroprosthesis for restoring bladder and bowel control to patients with spinal cord injuries: a multicenter trial. Arch Phys Med Rehabil 2001;82:1512–1519.
73. Creasey GH, Kilgore KL, Brown-Triolo DL, Dahlberg JE, Peckham PH, Keith MW. Reduction of costs of disability using neuroprostheses. Assist Technol 2000;12:67–75.
74. Dai R, Stein RB, Andrews BJ, James KB, Wieler M. Application of tilt sensors in functional electrical stimulation. IEEE Trans Rehabil Eng 1996;4:63–72.
75. Daly JJ, Roenigk K, Holcomb J, Rogers JM, Butler K, Gansen J, et al. A randomized controlled trial of functional neuromuscular stimulation in chronic stroke subjects. Stroke 2006; 37:172–178.
76. Daly JJ, Ruff RL, Haycook K, Strasshofer B, Marsolais EB, Dobos L. Feasibility of gait training for acute stroke patients using FNS with implanted electrodes. J Neurol Sci 2000;179: 103–107.
77. Davis JA Jr, Triolo RJ, Uhlir J, Bieri C, Rohde L, Lissy D, et al. Preliminary performance of a surgically implanted neuroprosthesis for standing and transfers—where do we stand? J Rehabil Res Dev 2001;38:609–617.
78. Davis R, Eckhouse R, Patrick JF, Delehanty A. Computer-controlled 22-channel stimulator for limb movement. Acta Neurochir (Wien) 1987;39S:117–120.
79. de Carvalho DC, Cliquet A Jr. Energy expenditure during rest and treadmill gait training in quadriplegic subjects. Spinal Cord 2005;43:658–663.
80. de Carvalho DC, Martins CL, Cardoso SD, Cliquet A. Improvement of metabolic and cardiorespiratory responses through treadmill gait training with neuromuscular electrical stimulation in quadriplegic subjects. Artif Organs 2006; 30:56–63.
81. Delitto A, Snyder-Mackler L. Two theories of muscle strength augmentation using percutaneous electrical stimulation. Phys Ther 1990;70:158–164.
82. Deuchert M, Ruben J, Schwiemann J, Meyer R, Thees S, Krause T, et al. Event-related fMRI of the somatosensory system using electrical finger stimulation. Neuroreport 2002; 13:365–369.
83. DiMarco AF, Onders RP, Ignagni A, Kowalski KE, Mortimer JT. Phrenic nerve pacing via intramuscular diaphragm electrodes in tetraplegic subjects. Chest 2005;127:671–678.
84. DiMarco AF, Takaoka Y, Kowalski KE. Combined intercostal and diaphragm pacing to provide artificial ventilation in patients with tetraplegia. Arch Phys Med Rehabil 2005;86: 1200–1207.
85. Dobelle WH, D'Angelo MS, Goetz BF, Kiefer DG, Lallier TJ, Lamb JI, et al. 200 cases with a new breathing pacemaker dispels myths about diaphragm pacing. Trans Am Soc Artif Intern Organs 1994;40:244–252.
86. Donaldson N, Rushton D, Tromans T. Neuroprostheses for leg function after spinal cord injury. Lancet 1997;350:711.
87. Douglas AJ, Walsh EG, Wright GW, Creasey GH, Edmond P. The effects of neuromuscular stimulation on muscle tone at the knee in paraplegia. Exp Physiol 1991;76:357–367.
88. Dupont A-C, Bagg SD, Creasey JL, Romano C, Romano D, Loeb GE, et al. Clinical trials of BION injectable neuromuscular stimulators. 6th Annual Conference of the International Functional Electrical Stimulation Society, Cleveland, OH; June 16–20, 2001.
89. Dupont Salter AC, Richmond FJ, Loeb GE. Prevention of muscle disuse atrophy by low-frequency electrical stimulation in rats. IEEE Trans Neural Syst Rehabil Eng 2003;11: 218–226.
90. Durfee WK, Rivard A. Design and simulation of a pneumatic, stored-energy, hybrid orthosis for gait restoration. J Biomech Eng 2005;127:1014–1019.
91. Edstrom L, Grimby L. Effect of exercise on the motor unit. Muscle Nerve 1986;9:104–126.
92. Egon G, Barat M, Colombel P, Visentin C, Isambert JL, Guerin J. Implantation of anterior sacral root stimulators combined with posterior sacral rhizotomy in spinal injury patients. World J Urol 1998;16:342–349.
93. Elefteriades JA, Quin JA, Hogan JF, Holcomb WG, Letsou GV, Chlosta WF, et al. Long-term follow-up of pacing of the conditioned diaphragm in quadriplegia. Pacing Clin Electrophysiol 2002;25:897–906.
94. Eser P, de Bruin ED, Telley I, Lechner HE, Knecht H, Stussi E. Effect of electrical stimulation-induced cycling on bone mineral density in spinal cord-injured patients. Eur J Clin Invest 2003;33:412–419.

95. Faghri PD, Rodgers MM, Glaser RM, Bors JG, Ho C, Akuthota P. The effects of functional electrical stimulation on shoulder subluxation, arm function recovery, and shoulder pain in hemiplegic stroke patients. Arch Phys Med Rehabil 1994;75:73–79.
96. Faghri PD, Van Meerdervort HF, Glaser RM, Figoni SF. Electrical stimulation-induced contraction to reduce blood stasis during arthroplasty. IEEE Trans Rehabil Eng 1997;5: 62–69.
97. Fasoli SE, Krebs HI, Hogan N. Robotic technology and stroke rehabilitation: translating research into practice. Top Stroke Rehabil 2004;11:11–19.
98. Ferrante S, Pedrocchi A, Ianno M, De Momi E, Ferrarin M, Ferrigno G. Functional electrical stimulation controlled by artificial neural networks: pilot experiments with simple movements are promising for rehabilitation applications. Funct Neurol 2004;19:243–252.
99. Fields RW. Electromyographically triggered electric muscle stimulation for chronic hemiplegia. Arch Phys Med Rehabil 1987;68:407–414.
100. Fodstad H. The Swedish experience in phrenic nerve stimulation. Pacing Clin Electrophysiol 1987;10:246–251.
101. Franceschini M, Baratta S, Zampolini M, Loria D, Lotta S. Reciprocating gait orthosis: a multicenter study of their use by spinal cord injured patients. Arch Phys Med Rehabil 1997;78:582–586.
102. Francisco G, Chae J, Chawla H, Kirshblum S, Zorowitz R, Lewis G, et al. Electromyogram-triggered neuromuscular stimulation for improving the arm function of acute stroke survivors: a randomized pilot study. Arch Phys Med Rehabil 1998;79:570–575.
103. Frey Law LA, Shields RK. Predicting human chronically paralyzed muscle force: a comparison of three mathematical models. J Appl Physiol 2006;100:1027–1036.
104. Fry AC, Allemeier CA, Staron RS. Correlation between percentage fiber type area and myosin heavy chain content in human skeletal muscle. Eur J Appl Physiol Occup Physiol 1994;68:246–251.
105. Gallien P, Brissot R, Eyssette M, Tell L, Barat M, Wiart L, et al. Restoration of gait by functional electrical stimulation for spinal cord injured patients. Paraplegia 1995;33:660–664.
106. Galvani L. Collezione delle Opera. Bologna, 1841. p 17–27.
107. Glenn WW, Brouillette RT, Dentz B, Fodstad H, Hunt CE, Keens TG, et al. Fundamental considerations in pacing of the diaphragm for chronic ventilatory insufficiency: a multicenter study. Pacing Clin Electrophysiol 1988;11:2121–2127.
108. Glenn WW, Hogan JF, Loke JS, Ciesielski TE, Phelps ML, Rowedder R. Ventilatory support by pacing of the conditioned diaphragm in quadriplegia. N Engl J Med 1984;310: 1150–1155.
109. Glenn WW, Hogan JF, Phelps ML. Ventilatory support of the quadriplegic patient with respiratory paralysis by diaphragm pacing. Surg Clin North Am 1980;60:1055–1078.
110. Glenn WW, Holcomb WG, Hogan J, Matano I, Gee JB, Motoyama EK, et al. Diaphragm pacing by radiofrequency transmission in the treatment of chronic ventilatory insufficiency. Present status. J Thorac Cardiovasc Surg 1973;66: 505–520.
111. Glenn WW, Phelps ML. Diaphragm pacing by electrical stimulation of the phrenic nerve. Neurosurgery 1985;17: 974–984.
112. Glenn WW, Sairenji H. Diaphragm pacing in the treatment of chronic ventilatory insufficiency. In: Roussos C, Macklem PT, editors. The thorax: lung biology in health and disease, Vol. 29. New York: Marcel Dekker; 1985. p 1407.
113. Goldstein LB. Neuropharmacology of TBI-induced plasticity. Brain Inj 2003;17:685–694.
114. Granat MH, Ferguson AC, Andrews BJ, Delargy M. The role of functional electrical stimulation in the rehabilitation of patients with incomplete spinal cord injury—observed benefits during gait studies. Paraplegia 1993;31:207–215.
115. Grandjean PA, Mortimer JT. Recruitment properties of monopolar and bipolar epimysial electrodes. Ann Biomed Eng 1986;14:53–66.
116. Graupe D, Kohn K. Functional electrical stimulation for ambulation by paraplegics. Malabar, FL: Krieger; 1994.
117. Gregory CM, Williams RH, Vandenborne K, Dudley GA. Metabolic and phenotypic characteristics of human skeletal muscle fibers as predictors of glycogen utilization during electrical stimulation. Eur J Appl Physiol 2005;95:276–282.
118. Grill WM, Mortimer JT. Neural and connective tissue response to long-term implantation of multiple contact nerve cuff electrodes. J Biomed Mater Res 2000;50:215–226.
119. Hainaut K, Duchateau J. Neuromuscular electrical stimulation and voluntary exercise. Sports Med 1992;14:100–113.
120. Han BS, Jang SH, Chang Y, Byun WM, Lim SK, Kang DS. Functional magnetic resonance image finding of cortical activation by neuromuscular electrical stimulation on wrist extensor muscles. Am J Phys Med Rehabil 2003;82:17–20.
121. Handa I, Matsushita N, Ihashi K, Yagi R, Mochizuki R, Mochizuki H, et al. A clinical trial of therapeutic electrical stimulation for amyotrophic lateral sclerosis. Tohoku J Exp Med 1995;175:123–134.
122. Handa Y, Handa T, Ichie M, Murakami H, Hoshimiya N, Ishikawa S, et al. Functional electrical stimulation (FES) systems for restoration of motor function of paralyzed muscles—versatile systems and a portable system. Front Med Biol Eng 1992;4:241–255.
123. Handa Y, Hoshimiya N. Functional electrical stimulation for the control of the upper extremities. Med Prog Technol 1987;12:51–63.
124. Handa Y, Hoshimiya N, Iguchi Y, Oda T. Development of percutaneous intramuscular electrode for multichannel FES system. IEEE Trans Biomed Eng 1989;36:706–710.
125. Hart RL, Kilgore KL, Peckham PH. A comparison between control methods for implanted FES hand-grasp systems. IEEE Trans Rehabil Eng 1998;6:208–218.
126. Hebb DO. The organization of behavior: a neuropsychological theory. New York: John Wiley & Sons; 1949.
127. Henneman E. Relation between size of neurons and their susceptibility to discharge. Science 1957;126:1345–1347.
128. Henneman E, Somjen G, Carpenter DO. Functional significance of cell size in spinal motoneurons. J Neurophysiol 1965;28:560–580.
129. Ho CL, Holt KG, Saltzman E, Wagenaar RC. Functional electrical stimulation changes dynamic resources in children with spastic cerebral palsy. Phys Ther 2006;86:987–1000.
130. Hodgkin A, Huxley, A. A quantitative description of ion currents and its applications to conduction and excitation in nerve membranes. J Physiol 1952;117:500–544.
131. Hodgkin A, Rushton WAH. The electrical constants of a crustacean nerve fibre. Proc R Soc Lond B 1946;133:444–479.
132. Hodgkin AL. The conduction of the nervous impulse. Springfield, IL: Thomas; 1964.
133. Hoffer JA, Loeb GE. Implantable electrical and mechanical interfaces with nerve and muscle. Ann Biomed Eng 1980;8: 351–360.
134. Hoffer JA, Stein RB, Haugland MK, Sinkjaer T, Durfee WK, Schwartz AB, et al. Neural signals for command control and feedback in functional neuromuscular stimulation: a review. J Rehabil Res Dev 1996;33:145–157.
135. Hooker SP, Scremin AM, Mutton DL, Kunkel CF, Cagle G. Peak and submaximal physiologic responses following electrical stimulation leg cycle ergometer training. J Rehabil Res Dev 1995;32:361–366.
136. Hunt CE, Brouillette RT, Weese-Mayer DE, Morrow A, Ilbawi MN. Diaphragm pacing in infants. Technique and results. Pacing Clin Electrophysiol 1988;11:2135–2141.
137. Ilbawi MN, Idriss FS, Hunt CE, Brouillette RT, DeLeon SY. Diaphragmatic pacing in infants: techniques and results. Ann Thorac Surg 1985;40:323–329.
138. Jacobs PL, Nash MS. Exercise recommendations for individuals with spinal cord injury. Sports Med 2004;34:727–751.

139. Jacobs PL, Nash MS, Klose KJ, Guest RS, Needham-Shropshire BM, Green BA. Evaluation of a training program for persons with SCI paraplegia using the Parastep 1 ambulation system: part 2. Effects on physiological responses to peak arm ergometry. Arch Phys Med Rehabil 1997;78:794–798.
140. Jaeger RJ, Yarkony GM, Smith RM. Standing the spinal cord injured patient by electrical stimulation: refinement of a protocol for clinical use. IEEE Trans Biomed Eng 1989;36: 720–728.
141. Jezernik S, Craggs M, Grill WM, Creasey G, Rijkhoff NJ. Electrical stimulation for the treatment of bladder dysfunction: current status and future possibilities. Neurol Res 2002; 24:413–430.
142. Johnson MW, Peckham PH. Evaluation of shoulder movement as a command control source. IEEE Trans Biomed Eng 1990;37:876–885.
143. Johnson MW, Peckham PH, Bhadra N, Kilgore KL, Gazdik MM, Keith MW, et al. Implantable transducer for two-degree of freedom joint angle sensing. IEEE Trans Rehabil Eng 1999;7:349–359.
144. Jostarndt-Fogen K, Puntschart A, Hoppeler H, Billeter R. Fibre-type specific expression of fast and slow essential myosin light chain mRNAs in trained human skeletal muscles. Acta Physiol Scand 1998;164:299–308.
145. Juch PJ, Minkels RF. The strap-electrode: a stimulating and recording electrode for small nerves. Brain Res Bull 1989; 22:917–918.
146. Kantor C, Andrews BJ, Marsolais EB, Solomonow M, Lew RD, Ragnarrson KT. Report on a conference on motor prostheses for workplace mobility of paraplegic patients in North America. Paraplegia 1993;31:439–456.
147. Kaplan RE, Czyrny JJ, Fung TS, Unsworth JD, Hirsh J. Electrical foot stimulation and implications for the prevention of venous thromboembolic disease. Thromb Haemost 2002;88: 200–204.
148. Kenney L, Bultstra G, Buschman R, Taylor P, Mann G, Hermens H, et al. An implantable two channel drop foot stimulator: initial clinical results. Artif Organs 2002;26:267–270.
149. Kern H, Salmons S, Mayr W, Rossini K, Carraro U. Recovery of long-term denervated human muscles induced by electrical stimulation. Muscle Nerve 2005;31:98–101.
150. Khaslavskaia S, Sinkjaer T. Motor cortex excitability following repetitive electrical stimulation of the common peroneal nerve depends on the voluntary drive. Exp Brain Res 2005; 162:497–502.
151. Kilgore KL, Bhadra N. Nerve conduction block utilising high-frequency alternating current. Med Biol Eng Comput 2004;42:394–406.
152. Kilgore KL, Peckham PH, Keith MW, Montague FW, Hart RL, Gazdik MM, et al. Durability of implanted electrodes and leads in an upper-limb neuroprosthesis. J Rehabil Res Dev 2003;40:457–468.
153. Kilgore KL, Peckham PH, Keith MW, Thrope GB. Electrode characterization for functional application to upper extremity FNS. IEEE Trans Biomed Eng 1990;37:12–21.
154. Kim JH, Manuelidis EE, Glen WW, Kaneyuki T. Diaphragm pacing: histopathological changes in the phrenic nerve following long-term electrical stimulation. J Thorac Cardiovasc Surg 1976;72:602–608.
155. Kim Y, Schmit BD, Youm Y. Stimulation parameter optimization for functional electrical stimulation assisted gait in human spinal cord injury using response surface methodology. Clin Biomech (Bristol, Avon) 2006;21:485–494.
156. Kimberley TJ, Lewis SM, Auerbach EJ, Dorsey LL, Lojovich JM, Carey JR. Electrical stimulation driving functional improvements and cortical changes in subjects with stroke. Exp Brain Res 2004;154:450–460.
157. Kleim JA, Barbay S, Nudo RJ. Functional reorganization of the rat motor cortex following motor skill learning. J Neurophysiol 1998;80:3321–3325.
158. Kljajic M, Malezic M, Acimovic R, Vavken E, Stanic U, Pangrsic B, et al. Gait evaluation in hemiparetic patients using subcutaneous peroneal electrical stimulation. Scand J Rehabil Med 1992;24:121–126.
159. Knutson JS, Hoyen HA, Kilgore KL, Peckham PH. Simulated neuroprosthesis state activation and hand-position control using myoelectric signals from wrist muscles. J Rehabil Res Dev 2004;41:461–472.
160. Knutson JS, Naples GG, Peckham PH, Keith WM. Electrode fracture rate and occurrences of infection and granuloma associated with percutaneous intramuscular electrodes in upper-limb functional electrical stimulation application. J Rehabil Res Dev 2003;39:671–684.
161. Kobayashi H, Onishi H, Ihashi K, Yagi R, Handa Y. Reduction in subluxation and improved muscle function of the hemiplegic shoulder joint after therapeutic electrical stimulation. J Electromyogr Kinesiol 1999;9:327–336.
162. Kobetic R, Marsolais EB. Synthesis of paraplegic gait with multichannel functional neuromuscular stimulation. IEEE Trans Biomed Eng 1994;2:66–67.
163. Kobetic R, Marsolais EB, Samane P, Borges G. The next step: artificial walking. In: Rose J, Ganble JG, editors. Human walking. Baltimore: Williams & Wilkins; 1994. p 225–252.
164. Kobetic R, Marsolais EB, Triolo RJ, Davy DT, Gaudio R, Tashman S. Development of a hybrid gait orthosis: a case report. J Spinal Cord Med 2003;26:254–258.
165. Kobetic R, Triolo RJ, Uhlir JP, Bieri C, Wibowo M, Polando G, et al. Implanted functional electrical stimulation system for mobility in paraplegia: a follow-up case report. IEEE Trans Rehabil Eng 1999;7:390–398.
166. Kraft GH, Fitts SS, Hammond MC. Techniques to improve function of the arm and hand in chronic hemiplegia. Arch Phys Med Rehabil 1992;73:220–227.
167. Krakauer JW. Motor learning: its relevance to stroke recovery and neurorehabilitation. Curr Opin Neurol 2006;19:84–90.
168. Kralj A, Bajd T. Functional electrical stimulation: standing and walking after spinal cord injury. Boca Raton, FL: CRC Press; 1989.
169. Kralj A, Bajd T, Kvesic Z, Turk R. Electrical stimulation of incomplete paraplegic patients/Proc 4th Annual RESNA Conference, Washington, DC; 1981.
170. Krebs HI, Volpe BT, Aisen ML, Hogan N. Increasing productivity and quality of care: robot-aided neuro-rehabilitation. J Rehabil Res Dev 2000;37:639–652.
171. Kubis HP, Hanke N, Scheibe RJ, Meissner JD, Gros G. Ca2+ transients activate calcineurin/NFATc1 and initiate fast-to-slow transformation in a primary skeletal muscle culture. Am J Physiol Cell Physiol 2003;285:C56–63.
172. Kubis HP, Scheibe RJ, Meissner JD, Hornung G, Gros G. Fast-to-slow transformation and nuclear import/export kinetics of the transcription factor NFATc1 during electrostimulation of rabbit muscle cells in culture. J Physiol (Lond) 2002;541:835–847.
173. Kugelberg E, Edstrom L. Differential histochemical effects of muscle contractions on phosphorylase and glycogen in various types of fibres: relation to fatigue. J Neurol Neurosurg Psychiatry 1968;31:415–423.
174. Lake DA. Neuromuscular electrical stimulation. An overview and its application in the treatment of sports injuries. Sports Med 1992;13:320–336.
175. Lapicque L. Recherches quantitatives sur l'excitation electrique des nerfs traitee comme une polarization. J Physiol Pathol Gen 1907;9:620–635.
176. Larsen JO, Thomsen M, Haugland M, Sinkjaer T. Degeneration and regeneration in rabbit peripheral nerve with long-term nerve cuff electrode implant: a stereological study of myelinated and unmyelinated axons. Acta Neuropathol (Berl) 1998;96:365–378.
177. Lauer RT, Peckham PH, Kilgore KL. EEG-based control of a hand grasp neuroprosthesis. Neuroreport 1999;10:1767–1771.
178. Lauer RT, Peckham PH, Kilgore KL, Heetderks WJ. Applications of cortical signals to neuroprosthetic control: a critical review. IEEE Trans Rehabil Eng 2000;8:205–208.

179. Leandri M, Parodi CI, Corrieri N, Rigardo S. Comparison of TENS treatments in hemiplegic shoulder pain. Scand J Rehabil Med 1990;22:69–71.
180. Lee RG, van Donkelaar P. Mechanisms underlying functional recovery following stroke. Can J Neurol Sci 1995;22: 257–263.
181. Leeds EM, Klose KJ, Ganz W, Serafini A, Green BA. Bone mineral density after bicycle ergometry training. Arch Phys Med Rehabil 1990;71:207–209.
182. Lemay MA, Crago PE, Keith MW. Restoration of pronosupination control by FNS in tetraplegia—experimental and biomechanical evaluation of feasibility. J Biomech 1996;29: 435–442.
183. Lertmanorat Z, Durand DM. Extracellular voltage profile for reversing the recruitment order of peripheral nerve stimulation: a simulation study. J Neural Eng 2004;1:202–211.
184. Levin MF, Hui-Chan CW. Relief of hemiparetic spasticity by TENS is associated with improvement in reflex and voluntary motor functions. Electroencephalogr Clin Neurophysiol 1992;85:131–142.
185. Lewek M, Stevens J, Snyder-Mackler L. The use of electrical stimulation to increase quadriceps femoris muscle force in an elderly patient following a total knee arthroplasty. Phys Ther 2001;81:1565–1571.
186. Li M. Electrical stimulation in the treatment of osteoporosis in sciatic denervated rat tibia. Zhonghua Wai Ke Za Zhi 1992;30:458–460, 508.
187. Lieberson W, Holmquest H, Scot D, Dow M. Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegia patients. Arch Phys Med Rehabil 1961;42:101–105.
188. Linn SL, Granat MH, Lees KR. Prevention of shoulder subluxation after stroke with electrical stimulation. Stroke 1999; 30:963–968.
189. Ljubicic V, Adhihetty PJ, Hood DA. Application of animal models: chronic electrical stimulation-induced contractile activity. Can J Appl Physiol 2005;30:625–643.
190. Loeb GE, Zamin CJ, Schulman JH, Troyk PR. Indictable microstimulator for functional electrical stimulation. Med Biol Eng 1991;29:NS13–NS19.
191. MacDonagh RP, Forster DM, Thomas DG. Urinary continence in spinal injury patients following complete sacral posterior rhizotomy. Br J Urol 1990;66:618–622.
192. MacDonagh RP, Sun WM, Smallwood R, Forster D, Read NW. Control of defecation in patients with spinal injuries by stimulation of sacral anterior nerve roots. BMJ 1990;300: 1494–1497.
193. Madersbacher H, Fischer J, Ebner A. Anterior sacral root stimulator (Brindley): experience especially in women with neurogenic urinary incontinence. Neurourol Urodyn 1988; 7:593–601.
194. Maimoun L, Fattal C, Micallef JP, Peruchon E, Rabischong P. Bone loss in spinal cord-injured patients: from physiopathology to therapy. Spinal Cord 2006;44:203–210.
195. Mansfield A, Lyons GM. The use of accelerometry to detect heel contact events for use as a sensor in FES assisted walking. Med Eng Phys 2003;25:879–885.
196. Marsolais EB, Kobetic R. Implantation technique and experience with percutaneous intramuscular electrodes in the lower extremities. J Rehab Res Dev 1986;23:1–8.
197. Marsolais EB, Kobetic R, Chizeck HJ, Jacobs JL. Orthoses and electrical stimulation for walking in complete paraplegics. J Neurorehab 1991;5:13–22.
198. Matheson GO, Dunlop RJ, McKenzie DC, Smith CF, Allen PS. Force output and energy metabolism during neuromuscular electrical stimulation: a 31P-NMR study. Scand J Rehabil Med 1997;29:175–180.
199. McDonald JW. Repairing the damaged spinal cord: from stem cells to activity-based restoration therapies. Clin Neurosurg 2004;51:207–227.
200. McNeal DR. Analysis of a model for excitation of myelinated nerve. IEEE Trans Biomed Eng 1976;23:329–337.
201. Memberg W PP, Keith MH. A surgically implanted intramuscular electrode for an implantable neuromuscular stimulation system. IEEE Trans Biomed Eng 1994;2:80–91.
202. Memberg WD, Peckham PH, Thorpe GB, Keith MW, Kicher TP. An analysis of the reliability of percutaneous intramuscular electrodes in upper extremity FNS applications. IEEE Trans Rehabil Eng 1993;1:126–132.
203. Merletti R, Acimovic R, Grobelnik S, Cvilak G. Electrophysiological orthosis for the upper extremity in hemiplegia: feasibility study. Arch Phys Med Rehabil 1975;56:507–513.
204. Merletti R, Zelaschi F, Latella D, Galli M, Angeli S, Sessa MB. A control study of muscle force recovery in hemiparetic patients during treatment with functional electrical stimulation. Scand J Rehabil Med 1978;10:147–154.
205. Merli GJ, Crabbe S, Paluzzi RG, Fritz D. Etiology, incidence, and prevention of deep vein thrombosis in acute spinal cord injury. Arch Phys Med Rehabil 1993;74:1199–1205.
206. Middleton JW, Yeo JD, Blanch L, Vare V, Peterson K, Brigden K. Clinical evaluation of a new orthosis, the 'walkabout', for restoration of functional standing and short distance mobility in spinal paralysed individuals. Spinal Cord 1997; 35:574–579.
207. Moe JH, Post HW. Functional electrical stimulation for ambulation in hemiplegia. J Lancet 1962;82:285–288.
208. Mollard JM, Prevot JM, Baulande M. [Prevention of deep venous thrombosis by physical methods. Use of an external electrical stimulator. Initial results in surgery of the hip]. Phlebologie 1985;38:293–305.
209. Mortimer JT. Motor prostheses. In: Brookhart JM, Mountcastle VB, editors. Handbook of physiology: the nervous system II. Bethesda, MD: American Physiolgical Society; 1981. p 155–187.
210. Nannini N, Horch K. Muscle recruitment with intrafascicular electrodes. IEEE Trans Biomed Eng 1991;38:769–776.
211. Naples GG, Mortimer JT, Scheiner A, Sweeney JD. A spiral nerve cuff electrode for peripheral nerve stimulation. IEEE Trans Biomed Eng 1988;35:905–916.
212. Nudo RJ, Milliken GW. Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. J Neurophysiol 1996;75: 2144–2149.
213. Nudo RJ, Plautz EJ, Frost SB. Role of adaptive plasticity in recovery of function after damage to motor cortex. Muscle Nerve 2001;24:1000–1019.
214. Nudo RJ, Plautz EJ, Frost SB. Role of adaptive plasticity in recovery of function after damage to motor cortex. Muscle Nerve 2001;24:1000–1019.
215. Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. Science 1996;272:1791–1794.
216. Ogino M, Shiba N, Maeda T, Iwasa K, Tagawa Y, Matsuo S, et al. MRI quantification of muscle activity after volitional exercise and neuromuscular electrical stimulation. Am J Phys Med Rehabil 2002;81:446–451.
217. Oostra K, Van Laere M, Scheirlinck B. Use of electrical stimulation in brain-injured patients: a case report. Brain Inj 1997;11:761–764.
218. Orlin MN, Pierce SR, Stackhouse CL, Smith BT, Johnston T, Shewokis PA, et al. Immediate effect of percutaneous intramuscular stimulation during gait in children with cerebral palsy: a feasibility study. Dev Med Child Neurol 2005;47:684–690.
219. Ott SM. Osteoporosis in women with spinal cord injuries. Phys Med Rehabil Clin N Am 2001;12:111–131.
220. Paillard T, Noe F, Passelergue P, Dupui P. Electrical stimulation superimposed onto voluntary muscular contraction. Sports Med 2005;35:951–966.
221. Peckham PH, Keith MW, Freehafer AA. Restoration of functional control by electrical stimulation in the upper extremity of the quadriplegic patient. J Bone Joint Surg [Am] 1988;70:144–148.

222. Peckham PH, Keith MW, Kilgore KL, Grill JH, Wuolle KS, Thrope GB, et al. Efficacy of an implanted neuroprosthesis for restoring hand grasp in tetraplegia: a multicenter study. Arch Phys Med Rehabil 2001;82:1380–1388.
223. Peckham PH, Knutson JS. Functional electrical stimulation for neuromuscular applications. Annu Rev Biomed Eng 2005;7:327–360.
224. Peckham PH, Mortimer JT, Marsolais EB. Alteration in the force and fatigability of skeletal muscle in quadriplegic humans following exercise induced by chronic electrical stimulation. Clin Orthop Relat Res 1976;114:326–333.
225. Peckham PH, Mortimer JT, Van Der Meulen JP. Physiologic and metabolic changes in white muscle of cat following induced exercise. Brain Res 1973;50:424–429.
226. Pekindil Y, Sarikaya A, Birtane M, Pekindil G, Salan A. 99mTc-sestamibi muscle scintigraphy to assess the response to neuromuscular electrical stimulation of normal quadriceps femoris muscle. Ann Nucl Med 2001;15:397–401.
227. Pette D, Muller W, Leisner E, Vrbova G. Time dependent effects on contractile properties, fibre population, myosin light chains and enzymes of energy metabolism in intermittently and continuously stimulated fast twitch muscles of the rabbit. Pflugers Arch 1976;364:103–112.
228. Phillips W, Burkett LN, Munro R, Davis M, Pomeroy K. Relative changes in blood flow with functional electrical stimulation during exercise of the paralyzed lower limbs. Paraplegia 1995;33:90–93.
229. Pitcher JB, Ridding MC, Miles TS. Frequency-dependent, bi-directional plasticity in motor cortex of human adults. Clin Neurophysiol 2003;114:1265–1271.
230. Plautz EJ, Milliken GW, Nudo RJ. Effects of repetitive motor training on movement representations in adult squirrel monkeys: role of use versus learning. Neurobiol Learn Mem 2000;74:27–55.
231. Popovic DB, Popovic MB, Sinkjaer T, Stefanovic A, Schwirtlich L. Therapy of paretic arm in hemiplegic subjects augmented with a neural prosthesis: a cross-over study. Can J Physiol Pharmacol 2004;82:749–756.
232. Popovic DB, Stein RB, Jovanovic KL, Dai R, Kostov A, Armstrong WW. Sensory nerve recording for closed-loop control to restore motor functions. IEEE Trans Biomed Eng 1993; 40:1024–1031.
233. Postans NJ, Granat MH. Effect of functional electrical stimulation, applied during walking, on gait in spastic cerebral palsy. Dev Med Child Neurol 2005;47:46–52.
234. Powell J, Pandyan AD, Granat M, Cameron M, Stott DJ. Electrical stimulation of wrist extensors in poststroke hemiplegia. Stroke 1999;30:1384–1389.
235. Price CI, Pandyan AD. Electrical stimulation for preventing and treating post-stroke shoulder pain: a systematic Cochrane review. Clin Rehabil 2001;15:5–19.
236. Quevedo AA, Cliquet Junior A. A paradigm for design of closed loop neuromuscular electrical stimulator control systems. Artif Organs 1995;19:280–284.
237. Quintern J, Riener R, Rupprecht S. Comparison of simulation and experiments of different closed-loop strategies for functional electrical stimulation: experiments in paraplegics. Artif Organs 1997;21:232–235.
238. Rebersek S, Vodovnik L. Proportionally controlled functional electrical stimulation of hand. Arch Phys Med Rehabil 1973;54:378–382.
239. Ridding MC, Rothwell JC. Afferent input and cortical organization: a study with magnetic stimulation. Exp Brain Res 1999;126:536–544.
240. Riess J, Abbas JJ. Adaptive neural network control of cyclic movements using functional neuromuscular stimulation. IEEE Trans Rehabil Eng 2000;8:42–52.
241. Rijkhoff NJ. Neuroprostheses to treat neurogenic bladder dysfunction: current status and future perspectives. Childs Nerv Syst 2004;20:75–86.
242. Riley DA, Allin EF. The effects of inactivity, programmed stimulation, and denervation on the histochemistry of skeletal muscle fiber types. Exp Neurol 1973;40:391–413.
243. Robinson LQ, Grant A, Weston P, Stephenson TP, Lucas M, Thomas DG. Experience with the Brindley anterior sacral root stimulator. Br J Urol 1988;62:553–557.
244. Rodgers MM, Glaser RM, Figoni SF, Hooker SP, Ezenwa BN, Collins SR, et al. Musculoskeletal responses of spinal cord injured individuals to functional neuromuscular stimulation-induced knee extension exercise training. J Rehabil Res Dev 1991;28:19–26.
245. Rose FD, Brooks BM, Rizzo AA. Virtual reality in brain damage rehabilitation: review. Cyberpsychol Behav 2005;8: 241–262.
246. Rushton D. Functional electrical stimulation and rehabilitation-an hypothesis. Med Eng Phys 2003;25:75–78.
247. Rushton DN, Brindley GS, Polkey CE, Browning GV. Implant infections and antibiotic-impregnated silicone rubber coating. J Neurol Neurosurg Psychiatry 1989;52:223–229.
248. Rushton W. A theory of the effects of fibre size in medullated nerve. J Physiol 1951;115:101–122.
249. Ruud Bosch JL, Groen J. Treatment of refractory urge urinary incontinence with sacral spinal nerve stimulation in multiple sclerosis patients. Lancet 1996;348:717–719.
250. Sabatier MJ, Stoner L, Mahoney ET, Black C, Elder C, Dudley GA, et al. Electrically stimulated resistance training in SCI individuals increases muscle fatigue resistance but not femoral artery size or blood flow. Spinal Cord 2006;44:227–233.
251. Saitoh E, Suzuki T, Sonoda S, Fujitani J, Tomita Y, Chino N. Clinical experience with a new hip-knee-ankle-foot orthotic system using a medial single hip joint for paraplegic standing and walking. Am J Phys Med Rehabil 1996;75:198–203.
252. Sheffler LR, Hennessey M, Naples GG, Chae J. Peroneal nerve stimulation versus an ankle foot orthosis for correction of footdrop in stroke: impact in functional ambulation. Neurorehabil Neural Repair 2006;20:355–360.
253. Sherry JE, Oehrlein KM, Hegge KS, Morgan BJ. Effect of burst-mode transcutaneous electrical nerve stimulation on peripheral vascular resistance. Phys Ther 2001;81:1183–1191.
254. Shimada Y, Hatakeyama K, Minato T, Matsunaga T, Sato M, Chida S, et al. Hybrid functional electrical stimulation with medial linkage knee-ankle-foot orthoses in complete paraplegics. Tohoku J Exp Med 2006;209:117–123.
255. Shimada Y, Sato K, Kagaya H, Konishi N, Miyamoto S, Matsunaga T. Clinical use of percutaneous intramuscular electrodes for functional electrical stimulation. Arch Phys Med Rehabil 1996;77:1014–1018.
256. Sieck GC, Prakash YS. Morphological adaptations of neuromuscular junctions depend on fiber type. Can J Appl Physiol 1997;22:197–230.
257. Simcox S, Parker S, Davis GM, Smith RW, Middleton JW. Performance of orientation sensors for use with a functional electrical stimulation mobility system. J Biomech 2005;38: 1185–1190.
258. Sinclair PJ, Davis GM, Smith RM, Cheam BS, Sutton JR. Pedal forces produced during neuromuscular electrical stimulation cycling in paraplegics. Clin Biomech (Bristol, Avon) 1996;11:51–57.
259. Sinkjaer T, Haugland M, Inmann A, Hansen M, Nielsen KD. Biopotentials as command and feedback signals in functional electrical stimulation systems. Med Eng Phys 2003;25: 29–40.
260. Smith B, Peckham PH, Keith MW, Roscoe DD. An externally powered, multichannel implantable stimulator for versatile control of paralyzed muscle. IEEE Trans Biomed Eng 1987; 34:499–508.
261. Smith BT, Betz RR, Mulcahey MJ, Triolo RJ. Reliability of percutaneous intramuscular electrodes for upper extremity functional neuromuscular stimulation in adolescents with C5 tetraplegia. Arch Phys Med Rehabil 1994;75:939–945.

262. Smith GV, Alon G, Roys SR, Gullapalli P. Functional MRI determination of a dose-response relationship to lower extremity neuromuscular electrical stimulation in healthy subjects. Exp Brain Res 2003;150:33–39.
263. Snels IA, Dekker JH, van der Lee JH, Lankhorst GJ, Beckerman H, Bouter LM. Treating patients with hemiplegic shoulder pain. Am J Phys Med Rehabil 2002;81:150–160.
264. Snoek GJ, Ijzerman MJ, in't Groen FA, Stoffers TS, Zilvold G. Use of the NESS Handmaster to restore hand function in tetraplegia. Spinal Cord 2000;38:244–249.
265. Solomonow M. Biomechanics and physiology of a practical functional neuromuscular stimulation powered walking orthosis for paraplegics. In: Stein RB, Peckham PH, Popovic DP, editors. Neural prostheses: replacing motor function after disease or disability. New York: Oxford University Press; 1992. p 202–232.
266. Solomonow M, Baratta RV, Hirokawa S. The RGO generation II: muscle stimulation powered orthosis as a practical walking system for paraplegics. Orthopaedics 1989;12:1309–1315.
267. Solomonow M, Reisin E, Aguilar E, Baratta RV, Best R, D'Ambrosia R. Reciprocating gait orthosis powered with electrical muscle stimulation (RGO II). Part II. Medical evaluation of 70 paraplegic patients. Orthopedics 1997;20:411–418.
268. Sonde L, Gip C, Ferneus S, Nilsson C, Viitanen M. Stimulation with low frequency (1/7 Hz) transcutaneous electrical nerve stimulation (Low-TENS) increases motor function of post-stroke hemiparetic arm. Scand J Rehabil Med 1998;30:95–99.
269. Sonde L, Kalimo H, Fernaeus SE, Viitanen M. Low TENS treatment on post-stroke paretic arm: a three-year follow-up. Clin Rehabil 2000;14:14–19.
270. Spiegel J, Tintera J, Gawehn J, Stoeter P, Treede RD. Functional MRI of human primary somatosensory and motor cortex during median nerve stimulation. Clin Neurophysiol 1999;110:47–52.
271. Stanic U, Acimovic-Janezic R, Gros N, Trnkoczy A, Bajd T, Kljajic M. Multichannel electrical stimulation for correction of hemiplegic gait. Methodology and preliminary results. Scand J Rehabil Med 1978;10:75–92.
272. Stefancic M, Rebersek M, Merletti R. The therapeutic effects of the Ljublijana functional electrical brace. Eur Medicophys 1976;12:1–9.
273. Stein RB, Nichols TR, Jhamandas J, Davis L, Charles D. Stable long-term recordings from cat peripheral nerves. Brain Res 1977;128:21–38.
274. Stevens JE, Mizner RL, Snyder-Mackler L. Neuromuscular electrical stimulation for quadriceps muscle strengthening after bilateral total knee arthroplasty: a case series. J Orthop Sports Phys Ther 2004;34:21–29.
275. Strange KD, Hoffer JA. Restoration of use of paralyzed limb muscles using sensory nerve signals for state control of FES-assisted walking. IEEE Trans Rehabil Eng 1999;7:289–300.
276. Sweeney JD, Mortimer JT. An asymmetric two electrode cuff for generation of unidirectionally propagated action potentials. IEEE Trans Biomed Eng 1986;33:541–549.
277. Szlavik RB, de Bruin H. The effect of stimulus current pulse width on nerve fiber size recruitment patterns. Med Eng Phys 1999;21:507–515.
278. Takebe K, Basmajian J. Gait analysis in stroke patients to assess treatments of foot-drop. Arch Phys Med Rehabil 1976;10:75–92.
279. Takebe K, Kukulka C, Narayan M, Milner M, Basmajian J. Peroneal nerve stimulator in rehabilitation of hemiplegic patients. Arch Phys Med Rehabil 1975;56:237–240.
280. Targan RS, Alon G, Kay SL. 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 2000;122:246–252.
281. Taub E, Uswatt G. Constraint-Induced Movement therapy: answers and questions after two decades of research. Neurorehabilitation 2006;21:93–95.
282. Taylor P, Burridge J, Dunkerley A, Wood D, Norton J, Singleton C, et al. Clinical audit of 5 years provision of the Odstock dropped foot stimulator. Artif Organs 1999;23:440–442.
283. Taylor PN, Burridge JH, Dunkerley AL, Wood DE, Norton JA, Singleton C, et al. Clinical use of the Odstock dropped foot stimulator: its effect on the speed and effort of walking. Arch Phys Med Rehabil 1999;80:1577–1583.
284. Thoma H, Gerner H, Holle J, Kluger P, Mayr W, Meister B, et al. The phrenic pacemaker: substitution of paralyzed functions in tetraplegia. Trans Am Soc Artif Intern Organs 1987;33:472–479.
285. Tong KY, Mak AF, Ip WY. Command control for functional electrical stimulation hand grasp systems using miniature accelerometers and gyroscopes. Med Biol Eng Comput 2003;41:710–717.
286. Triolo RJ, Bieri C, Uhlir J, Kobetic R, Scheiner A, Marsolais EB. Implanted FNS systems for assisted standing and transfers for individuals with cervical spinal cord injuries. Arch Phys Med Rehabil 1996;7:1119–1128.
287. Uhlir JP, Triolo RJ, Kobetic R. The use of selective electrical stimulation of the quadriceps to improve standing function in paraplegia. IEEE Trans Rehabil Eng 2000;8:514–522.
288. van der Aa HE, Alleman E, Nene A, Snoek G. Sacral anterior root stimulation for bladder control: clinical results. Arch Physiol Biochem 1999;107:248–256.
289. Van Kerrebroeck PE, Koldewijn EL, Debruyne FM. Worldwide experience with the Finetech-Brindley sacral anterior root stimulator. Neurourol Urodyn 1993;12:497–503.
290. Van Kerrebroeck PE, Koldewijn EL, Rosier PF, Wijkstra H, Debruyne FM. Results of the treatment of neurogenic bladder dysfunction in spinal cord injury by sacral posterior root rhizotomy and anterior sacral root stimulation. J Urol 1996;155:1378–1381.
291. Van Kerrebroeck PEV, Kolewijn EL, Wijkstra H, Debruyne FMJ. Urodynamic evaluation before and after intradural posterior sacral rhizotomies and implantation of the Finetech-Brindley anterior sacral root stimulator. Urodinamica 1992;1:7–12.
292. Van Ouwenaller C, Laplace PM, Chantraine A. Painful shoulder in hemiplegia. Arch Phys Med Rehabil 1986;67:23–26.
293. Vanderlinden RG, Epstein SW, Hyland RH, Smythe HS, Vanderlinden LD. Management of chronic ventilatory insufficiency with electrical diaphragm pacing. Can J Neuro Sci 1988;15:63–67.
294. Vanderthommen M, Depresseux JC, Dauchat L, Degueldre C, Croisier JL, Crielaard JM. Spatial distribution of blood flow in electrically stimulated human muscle: a positron emission tomography study. Muscle Nerve 2000;23:482–489.
295. Veltink PH, Franken HM, Van Alste JA, Boom HB. Modelling the optimal control of cyclical leg movements induced by functional electrical stimulation. Int J Artif Organs 1992;15:746–755.
296. Vodovnik L, Rebersek S. Information content of myo-control signals for orthotic and prosthetic systems. Arch Phys Med Rehabil 1974;55:52–56.
297. Wang RY, Chan RC, Tsai MW. Functional electrical stimulation on chronic and acute hemiplegic shoulder subluxation. Am J Phys Med Rehabil 2000;79:385–390.
298. Wang RY, Yang YR, Tsai MW, Wang WT, Chan RC. Effects of functional electric stimulation on upper limb motor function and shoulder range of motion in hemiplegic patients. Am J Phys Med Rehabil 2002;81:283–290.
299. Waters R, McNeal D, Perry J. Experimental correction of footdrop by electrical stimulation of the peroneal nerve. J Bone Joint Surg 1975;57A:1047–1054.

300. Waters RL, Campbell JM, Nakai R. Therapeutic electrical stimulation of the lower limb by epimysial electrodes. Clin Orthop Relat Res 1988:44–52.
301. Waters RL, McNeal DR, Faloon W, Clifford B. Functional electrical stimulation of the peroneal nerve for hemiplegia. Long-term clinical follow-up. J Bone Joint Surg Am 1985;67: 792–793.
302. Weber DJ, Stein RB, Chan KM, Loeb G, Richmond F, Rolf R, et al. BIONic WalkAide for correcting foot drop. IEEE Trans Neural Syst Rehabil Eng 2005;13:242–246.
303. Weber DJ, Stein RB, Chan KM, Loeb GE, Richmond FJ, Rolf R, et al. Functional electrical stimulation using microstimulators to correct foot drop: a case study. Can J Physiol Pharmacol 2004;82:784–792.
304. Wielink G, Essink-Bot ML, van Kerrebroeck PE, Rutten FF. Sacral rhizotomies and electrical bladder stimulation in spinal cord injury. 2. Cost-effectiveness and quality of life analysis. Dutch Study Group on Sacral Anterior Root Stimulation. Eur Urol 1997;31:441–446.
305. Winstein CJ, Miller JP, Blanton S, Taub E, Uswatte G, Morris D, et al. Methods for a multisite randomized trial to investigate the effect of constraint-induced movement therapy in improving upper extremity function among adults recovering from a cerebrovascular stroke. Neurorehabil Neural Repair 2003;17:137–152.
306. Wolpaw JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM. Brain-computer interfaces for communication and control. Clin Neurophysiol 2002;113:767–791.
307. Wong AM, Su TY, Tang FT, Cheng PT, Liaw MY. Clinical trial of electrical acupuncture on hemiplegic stroke patients. Am J Phys Med Rehabil 1999;78:117–122.
308. Wuolle KS, Bryden AM, Peckham PH, Murray PK, Keith M. Satisfaction with upper-extremity surgery in individuals with tetraplegia. Arch Phys Med Rehabil 2003;84:1145–1149.
309. Yan T, Hui-Chan CW, Li LS. Functional electrical stimulation improves motor recovery of the lower extremity and walking ability of subjects with first acute stroke: a randomized placebo-controlled trial. Stroke 2005;36:80–85.
310. Yarkony GM, Jaeger RJ, Roth E, Kralj A, Quintern J. Functional neuromuscular stimulation for standing after spinal cord injury. Arch Phys Med Rehabil 1990;71:201–206.
311. Yu DT, Chae J, Walker ME, Kirsteins A, Elovic EP, Flanagan SR, et al. Intramuscular neuromuscular electrical stimulation for post-stroke shoulder pain: a multi-center randomized clinical trial. Arch Phys Med Rehabil 2004;85:695–704.
312. Zebedin E, Sandtner W, Galler S, Szendroedi J, Just H, Todt H, et al. Fiber type conversion alters inactivation of voltage-dependent sodium currents in murine C2C12 skeletal muscle cells. Am J Physiol Cell Physiol 2004;287:C270–280.
313. Zicot M, Rigaux P. [Effect of the frequency of neuromuscular electric stimulation of the leg on femoral arterial blood flow]. J Mal Vasc 1995;20:9–13.