Motor Neuroprostheses

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ABSTRACT

Neuroprostheses (NPs) are electrical stimulators that activate nerves, either to provide sensory input to the central nervous system (sensory NPs), or to activate muscles (motor NPs: MNPs). The first MNPs were belts with inbuilt batteries and electrodes developed in the 1850s to exercise the abdominal muscles. They became enormously popular among the general public, but as a result of exaggerated therapeutic claims they were soon discredited by the medical community. In the 1950s, MNPs reemerged for the serious purpose of activating paralyzed muscles. Neuromuscular electrical stimulation (NMES), when applied in a preset sequence, is called therapeutic electrical stimulation (TES). NMES timed so that it enhances muscle contraction in intended voluntary movements is called functional electrical stimulation (FES) or functional neuromuscular stimulation (FNS). It has been 50 years since the first FES device, a foot-drop stimulator, was described and 40 years since the first implantable version was tested in humans. A commercial foot-drop stimulator became available in the 1970s, but for various reasons, it failed to achieve widespread use. With advances in technology, such devices are now more convenient and reliable. Enhancing upper limb function is a more difficult task, but grasp-release stimulators have been shown to provide significant benefits. This chapter deals with the technical aspects of NMES, the therapeutic and functional benefits of TES and FES, delayed-onset and carryover effects attributable to "neuromodulation" and the barriers and opportunities in this rapidly developing field. © 2019 American Physiological Society. *Compr Physiol* 9:127-148, 2019.

Didactic Synopsis

Major teaching points

1. *Brief history of electrical stimulation of the nervous system.* Electrical stimulation of human peripheral nerves with the use of electrostatic machines for clinical purposes began in the 17th century but only began to be properly understood and applied in the 20th century.

2. *Basic mechanisms and methods of electrical stimulation with neural prostheses (NPs).* Methods: Trains of current pulses are applied either with stimulators external to the body connected through pad electrodes applied to the skin, or via implanted stimulators and wire electrodes terminating near or on peripheral nerves or within the central nervous system. Mechanisms: control of the recruitment of nerve axons depends on the amount of charge delivered per current pulse.

3. *Tissue interfaces (surface or implanted electrodes), corrosion, tissue reactions.* Electrode corrosion and inflammatory reactions of bodily tissues can occur, depending on the type of electrode, the current and duration of pulses delivered, and whether the pulses are monophasic or biphasic.

4. *Types of motor NPs.* MNPs either deliver fixed sequences of stimulation for exercise and retraining purposes (therapeutic electrical stimulation: TES), or stimulation triggered by biomechanical events or the user's own electromyographic activity to augment muscle contractions in exercise training, or in functional tasks (functional electrical stimulation: FES).

5. *Lower and upper limb MNPs.* Various designs of surface and implanted MNPs have been developed and commercialized to stimulate paralyzed muscles. Influential metastudies have concluded that FES may improve walking, balance, and range of motion in hemiplegic people and those with spinal cord injury.

6. *Respiratory MNPs, MNPs for bladder control.* There is a surprisingly long history of attempts to stimulate the phrenic nerve for respiration, and various nerves innervating or reflexly affecting the bladder and external urethral sphincter to restore control over micturition. Implanted stimulators for respiration and bladder control are available commercially.

7. *Epidural and intraspinal stimulators.* Epidural stimulation of the spinal cord via electrode arrays placed on the dorsal dura mater, originally developed to treat chronic pain, is

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increasingly being used to restore upper and lower limb movements. Intraspinal stimulation targeting motoneuron pools activating limb muscles or spinal cord nuclei controlling micturition is still in the experimental stages.

8. *Carry-over therapeutic effects and mechanisms.* Beneficial carryover effects lasting up to a few hours are commonly observed after sessions of TES or FES. In some NP applications, long-lasting beneficial effects develop slowly, over days or weeks, and may become permanent.

9. *Barriers to MNP technology transfer.* TES stimulators have become inexpensive consumer products, and are widely used. FES devices are much more expensive, because they incorporate sensors and control logic, they are designed to be wearable in daily life, and they are subjected to more stringent regulatory testing. The lack of governmental reimbursement of the cost of FES devices is a major barrier to their widespread use.

Introduction

In the 18th century, it was discovered that muscles were activated by nerves through a mechanism involving electricity (43). It had been known since antiquity that bodily contact with specialized marine creatures such as the electric torpedo ray could result in sudden, intense muscle contractions, sensation, and subsequent numbing of the affected body part (300). Some reports indicated that the shocks could be transmitted at a distance through water or metal. Numerous documents from Greek, Roman and Mediaeval times describe the intentional application of torpedo rays to the human body for therapeutic purposes (300). Various theories were proposed to explain how torpedo rays delivered these shocks but the true explanation had to await the gradual understanding and harnessing of electricity in the 17th and 18th centuries (42, 43). It had been known for centuries that when amber is rubbed vigorously with fur or cloth, light objects like feathers are attracted to it, and sparks can cross between the materials. In fact, a study of this phenomenon, which later was attributed to the separation and accumulation of electrostatic charge, led William Gilbert in his famous book De Magnete, to coin the word electricus, derived from the Greek word for amber, elektron (21, 42). In the 17th century, mechanical devices began to appear that generated electrostatic charge at the turn of a handle. In 1709, the basic design of many subsequent electrostatic generators had been established (42). These devices, used in conjunction with Leyden Jars, the precursors of capacitors, provided experimentalists and clinicians with the means to stimulate the nervous system.

Clinicians were soon making muscles in paralyzed people twitch by stimulating nerves with static electricity passed through the skin (175, 191). Faraday's invention of the induction coil in the mid-19th century made it possible to deliver trains of stimuli to nerves and muscles. This procedure, now known as neuromuscular electrical stimulation (NMES), soon became a means of experimentally stimulating peripheral nerves, the spinal cord, and the brain. The first atlas of motor points, that is, locations on the skin surface through which faradic stimulation activated muscles at the lowest thresholds, was published in 1867 (77). Countless neurophysiological studies using electrical stimulation followed, notably those on nerve conduction (126), the motor and sensory areas of the brain (86, 95, 228), spinal reflexes and locomotion (275), synaptic transmission (48), and many more.

By the end of the 19th century, the precursor of today's "Abs stimulator," the Pulvermacher/Harness Electropathic Belt, was being sold in large numbers to the public. The building in which these devices were manufactured and sold still stands at 52 Oxford St. London. The "Electreat" was another such device sold in the hundreds of thousands in the United States until the 1930s (151). At first, the medical community expressed a guarded interest in the clinical use of electrical stimulation (34), but in due course, the unrealistic therapeutic benefits claimed for devices like Pulvermacher's Belt led to their demise (78).

It was not until the 1950s that clinical interest in therapeutic electrical stimulation revived. This followed the invention of the transistor, which gave rise to convenient, portable stimulators and made it feasible to implant certain types of stimulator inside the body. All existing NPs are based on precursors developed between 1957 and 1972: cochlear implants (75, 76), foot-drop stimulators (144, 174); cardiac pacemakers (113), spinal cord epidural stimulators (273), phrenic nerve and diaphragm pacers (13, 146, 307), sacral nerve stimulators (45), and intraspinal stimulators (94, 213).

Millions of people worldwide live with neuromuscular weakness (paresis) or paralysis. It is possible to re-activate them electrically, either by stimulating the motor axons in the peripheral nerves that innervate them, sensory axons in these or other nerves that activate them reflexly, or central nervous system structures such as the motor cortex and spinal cord. However, there are numerous barriers to doing this in a way that improves motor function. The main problems are (i) selectivity: stimulating only those specific nerves that activate the paralyzed muscles, given that the nerves often lie deep within bodily tissues, under more superficial nerves that innervate non-targeted organs. Stimulation within brain and spinal cord networks often excites muscles additional to those targeted, as well as eliciting unwanted reflex responses; (ii) control: stimulating each neural structure at the right time and at the right strength; (iii) avoiding muscle fatigue; (iv) ensuring long-term reliability: maintaining a stable interface between electrodes and neural structures for many years; (v) avoiding damage: neurons in the peripheral and central nervous system are delicate and can be irreversibly damaged by electrolytic processes at the electrode interface and by mechanical strain caused by nerve cuffs and penetrating microelectrodes. (vi) While it is possible to activate denervated muscles directly through surface electrodes, the amplitudes of the electrical pulses required are about ten times those needed in normally innervated muscles, resulting in unacceptable levels of pain

in most cases (153). Nonetheless, in a population of people with SCI who had no local sensation, home-based electrical stimulation of denervated muscles over a long period of time was used successfully to restore muscle bulk and contractile force (7, 152).

Neuroprostheses: History, Definitions, and Scope

The term neural prosthesis originated in 1968 with the formation in London, UK of the MRC Neurological Prosthesis Unit, headed by Giles Brindley. The focus was on a visual cortical stimulator to restore sight in the blind. In 1970, the NIH formed the Sensory Prosthesis Program, also focusing on the restoration of vision with implanted cortical stimulation. In 1971, Terry Hambrecht and Tom Mortimer broadened the scope of this program to include motor function and the name was changed to the NIH Neural Prosthesis Program. The first annual Neural Prosthesis Workshop took place that year, and at the 1973 workshop, the technical challenges in developing a stimulator to restore hearing were discussed (60). The word neuroprosthesis first appeared in the literature in 1971 in relation to a spinal cord stimulator for bladder voiding (94, 212).

Brindley, Hambrecht, Mortimer and other pioneers in the field all used the term neuroprosthesis to describe a device that stimulated nerves electrically to produce a sensory or motor effect. In more recent years, electrical signals recorded from the brain or from muscles have been used to control computers and mechanical devices such as robot arms. It could certainly be argued that when an artificial limb or exoskeleton attached to the body (a prosthesis) is controlled by neural signals, the system should be called a neuroprosthesis, but this is not the generally accepted usage in the literature. Accordingly, in this article, the term motor neuroprostheses (MNPs) is restricted to devices in which electrical stimulation of nervous tissue is used to restore movement.

Basic Mechanisms

Neural control of muscle force

Mammalian muscles vary widely in their morphology and the number of alpha motoneuron axons in the muscle nerve innervating them (185). They also contain large numbers of sensory afferent axons as well as gamma motoneurons that innervate muscle spindles (140, 250). An alpha motoneuron and the muscle fibers it innervates is called a motor unit. In voluntary contractions, alpha motoneurons are recruited in ascending order of size (127, 128). In voluntary and reflex contractions, small alpha motoneurons that activate slow-twitch, low-force, fatigue-resistant motor units are recruited first, as they are more sensitive to excitatory synaptic currents. Large alpha motoneurons innervating fast-twitch, high-force, rapidly fatiguing muscle fibers are recruited last (51). This means that small fatigue-resistant motor units are recruited in steady contractions requiring low forces while large motor units that produce more force but fatigue rapidly, are recruited in strong, intermittent contractions. The orderly recruitment from small to large motoneurons is called Henneman's size principle (128).

Activating nerves and muscles electrically

An action potential is elicited in a nerve axon when a rapid change of voltage along the axon changes the distribution of charge across the cell membrane, reducing the transmembrane potential to a threshold value that triggers an action potential. This is achieved either by delivering a small, long-duration current pulse, or a large, short-duration current pulse between two electrodes near the axon (201, 202). The term "rheobase" is used to describe the level of current in a long-duration pulse that just activates a nerve. The companion term "chronaxie" is the duration of a pulse at twice the rheobase current, that just activates the nerve.

The strength of nerve stimulation can be varied by controlling the current, voltage, duration, or rate of pulses using feedback-controlled pulse generators. When the current is controlled, the current in each pulse has a specific time course, which ensures that the same number of nerve axons is activated, regardless of the interface impedance. If the interface impedance rises, for example due to poor electrode contact, the voltage automatically increases, forcing the same current through a smaller surface area. However, areas of high current density at the electrode-tissue interface can cause tissue irritation and damage. Regulatory agencies require that above a certain interface impedance, current-controlled stimulators must limit their voltage or shut down. When the voltage is controlled, the voltage in each pulse has a specific time course. If the interface impedance rises, less current flows, which avoids tissue damage, but fewer nerve axons are activated. In pulse-rate-controlled stimulators, the current or voltage per pulse is set to a constant level and the pulse rate is varied. Muscle force increases with motor unit firing rate, but the relationship is nonlinear. At low rates (10-25 pulses/s), muscle twitch forces are only partly fused, producing force ripple. Between 25 and 40 pulses/s, the contractions are smooth. Above 40 pulses/s, little further increase in muscle force is obtained and the muscle fatigues more rapidly (180). In pulse-width-controlled stimulators, the current or voltage per pulse is kept constant and the duration of the pulse is varied, typically in the range 50 to 500 microseconds.

The physiological recruitment order from small, fatigue-resistant motor units to large, fatigable motor units does not occur when peripheral nerves innervating muscles are stimulated. When a rapidly changing voltage is applied to a peripheral nerve, the larger the axon diameter the lower its threshold. Thus, less voltage is required to electrically activate the axons of large motoneurons than those of small motoneurons in the nerve, which is the reverse of the natural recruitment order. The reversal is incomplete, because the activation threshold

of axons also depends on their location within a nerve. Even so, the sub-optimal recruitment order, and the synchronous activation of motoneurons results in electrically activated muscles fatiguing more rapidly than voluntarily activated muscles (28).

Muscle spindle group Ia afferents synaptically activate synergistic motoneurons. Progressively increasing the number and firing rate of these afferents, as occurs when muscles are stretched, activates motoneurons in the normal physiological recruitment order. Group Ia afferent axons in muscle nerves have a slightly lower electrical threshold than motoneuron axons, so at low stimulus strengths only the afferent axons are activated and motoneurons are recruited synaptically according to the size principle (237). However, the orderly recruitment tends to break down once motoneuronal axons begin to be excited directly. H-reflex studies indicate that this transition occurs at low levels of muscle activation (137), at forces that are probably insufficient for most functional tasks of daily life.

Muscle contractions elicited by epidural spinal cord stimulation and intraspinal microstimulation (ISMS) show much less fatigue than contractions elicited by peripheral nerve stimulation, presumably again because motoneurons are recruited synaptically according to the size principle (145, 169, 209). This is because Ia afferent axons have a lower threshold to both epidural stimulation and ISMS than motoneuron cell bodies or axons (106, 256). With increasing epidural and ISMS amplitude, descending axons and propriospinal interneurons are presumably progressively activated, some of which would activate motoneurons synaptically. Finally, it is possible that ISMS directly activates motoneuron cell bodies according to the size of their cell bodies.

Electrical stimuli activate motoneurons synchronously whereas in voluntary contractions, motoneurons fire asynchronously. Asynchronous motor unit firing produces fused muscle contractions that are both stronger and more fatigue-resistant than those resulting from synchronous motor unit firing. Fifty years ago, it was shown that by subdividing ventral roots and supplying stimulating pulses to different groups of motor units in rotation, smooth contractions of soleus muscle could be obtained with low rates of stimulation and consequently, there was better fatigue resistance (255). Efforts are underway to reproduce this effect in MNPs by applying stimulation at two or more motor points and at sites that elicit stretch reflexes (28, 243).

Interestingly, optical stimulation of nerves in transgenic mice results in a normal, asynchronous, physiological recruitment order (177). The genetic manipulation required rules this specific method out as a clinical modality, but alternative optical stimulation strategies are being pursued (24, 233).

Methods of delivering stimuli to nerves

NPs have one of three basic designs: (i) a surface stimulator (external pulse generator: EPG) that delivers current pulses through the skin (i.e. "transcutaneously") via pairs of non-invasive surface electrodes; (ii) an EPG that delivers current pulses via one or more electrodes that *pass through* the skin; and (iii) an implanted pulse generator (IPG) that delivers current pulses percutaneously via implanted electrodes. The IPG receives commands, and in some cases, electrical energy, from an external wireless controller.

Several of the most widely used NPs are designed to stimulate sensory nerves. These include transcutaneous electrical nerve stimulators, cochlear stimulators, spinal cord epidural stimulators, sacral nerve stimulators, and vagus nerve stimulators. Sensory NPs will be mentioned in this article when their design features or the barriers they have to overcome are similar to those of motor NPs (MNPs).

The first type of MNP (Fig. 1A), the modern descendant of Pulvermacher's Electropathic Belt, is widely used by the general public and also by therapists, to increase muscle bulk and strength. The EPG typically delivers trains of current pulses transcutaneously, 2 to 20 mA in amplitude, 100 to 300 microseconds in duration at rates of 20 to 50 pulses/second, for up to an hour a day through surface electrodes. These typically comprise 1 to 25 cm^2 conductive patches of metal, carbonized rubber, or a conductive film printed on a flexible substrate, with an interface of self-adhesive hydrogel or moistened material. The interface traps water and dissolved ions and conforms to the small irregularities in the skin surface, thus maximizing contact area and minimizing impedance. In cheaper electrodes, the connecting leads terminate in small metal studs in the center of the conductive patch, resulting in a nonuniform current density that is high under the stud and falls away toward the edges of the electrode. The leads in higher-quality electrodes terminate in metal mesh or conductive film of the same area as the gel, resulting in a uniform current density. The electrodes are stuck to the skin or secured with straps, belts, or cuffs. The electrode delivering the negative-going phase of each current pulse, the cathodic electrode, is located over a motor point. The anodic electrode, also referred to as the "reference" or "indifferent" electrode, is located nearby. The motor point of a muscle is the place on the skin that overlies or is close to the nerve entry point.

The second type of MNP (Fig. 1B) delivers cathodic current pulses from an EPG through one or more insulated leads that pass through the skin (percutaneous electrodes). A surface electrode acts as the anodic, or reference, electrode. The leads are either implanted through percutaneous cannulae, or they are surgically placed with their conductive delivery ends attached to nerves by means of a nerve cuff, or anchored to the epimysium of target muscles by sutures or tines. In a multichannel system, pulses are interleaved and distributed to different muscle nerves in a cyclical order. The leads emerge through the skin and their conductive receiving ends terminate in a connector attached to the skin with a self-adhesive plastic film such as Tegaderm™, or Opsite™. With daily cleaning and maintenance, percutaneous electrodes can stay in place for months and even years (181, 182, 299). NPs based on

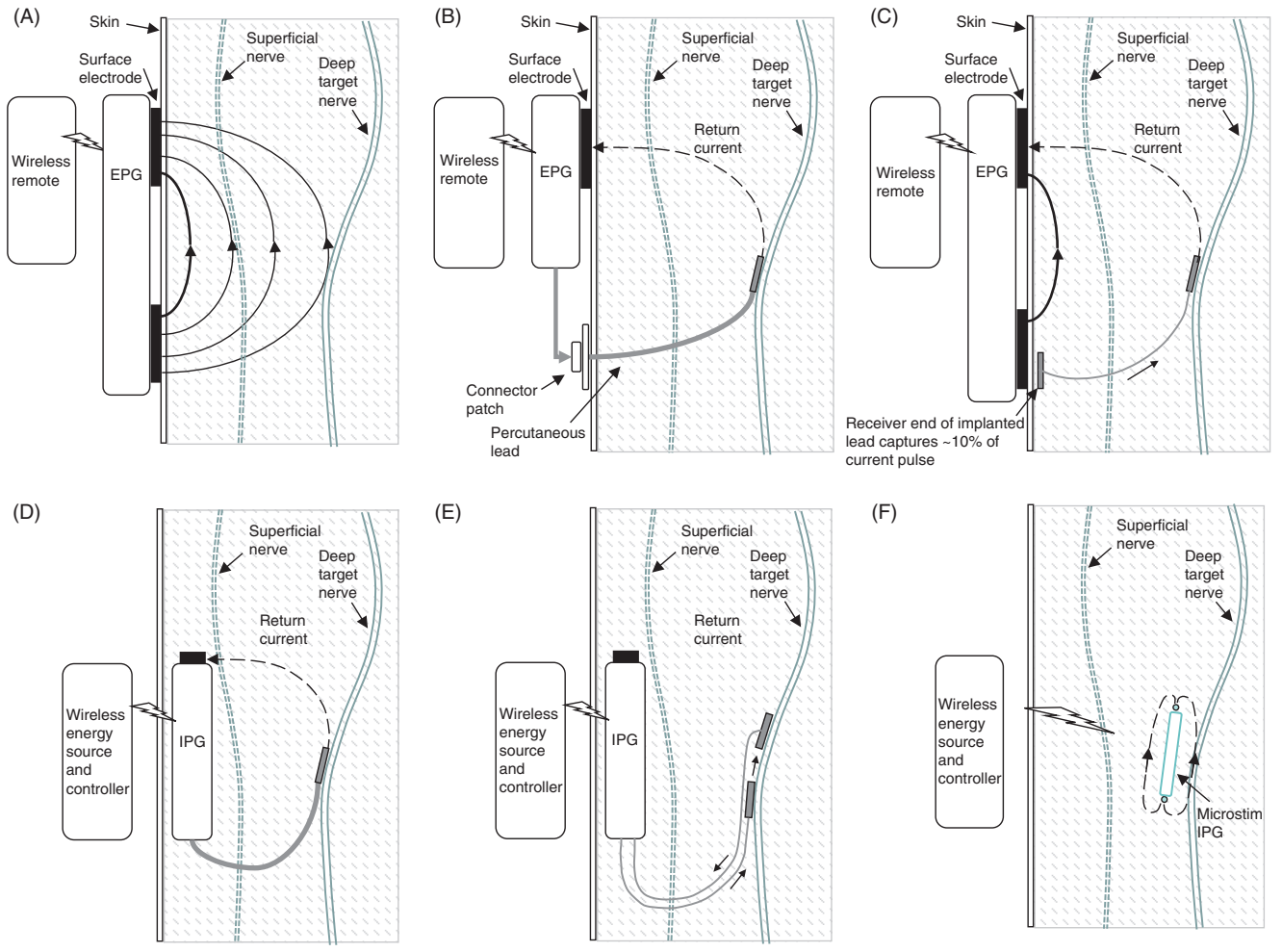

Figure 1 Basic designs of neural prostheses. (A) A surface stimulator (external pulse generator: EPG) delivers current pulses through the skin via a pair of surface electrodes. In some cases, a wireless controller controls the EPG. (B) An EPG delivers current pulses via one or more conductors, typically insulated wires that pass through the skin and terminate close to or on the nerve. The return current flows through the tissues to a surface (reference) electrode. (C) An EPG delivers current pulses through the skin via a pair of surface electrodes and some of the current is intercepted and "picked up" by a fully implanted lead, which delivers this current to the nerve. (D) An implanted pulse generator (IPG) receives energy and commands wirelessly through the skin and delivers current pulses to the nerve via an electrode. The return current flows through the tissues to a reference electrode on the body of the IPG. (E) An implanted pulse generator (IPG) receives energy and commands wirelessly through the skin and delivers current pulses to the nerve via a pair of electrodes. (F) An injectable microstimulator receives energy and commands wirelessly through the skin and delivers current pulses to the nerve through two conductive terminals on the body of the stimulator.

percutaneous leads are suitable for short-term applications. They are typically used to test the positioning of leads before an IPG is implanted and attached to them. They have also been useful in the research and testing phases of MNP development (5, 181, 241). They are currently used in the NeuRx diaphragm pacer (286) (see Respiratory MNPs).

The third type of NP (Fig. 1D-F) comprises an IPG, implanted leads and an external controller that supplies energy and commands to the IPG through the skin via a radio-frequency link. This basic design is used in sensory NPs such as the cochlear stimulator and spinal cord stimulator and has been implanted in hundreds of thousands of people (250). In the configuration of Figure 1D, a nerve is activated by a single electrode, the return current to the IPG flowing through bodily tissues to a reference electrode that is part of the casing of the IPG. Figure 1E shows a bipolar configuration in which pairs of leads deliver current to the target nerve. Figure 1F shows a microstimulator version in which each end of the stimulator has a conductive cap that takes the place of a conventional implanted lead.

Figure 1C shows a hybrid NP that combines an EPG with an implanted lead. As in type 1, the EPG delivers trains of current pulses transcutaneously through a pair of surface electrodes. As in type 3, the lead is fully implanted, with one conductive receiving end in subcutaneous tissue under the cathodic surface electrode and the other conductive delivery end in proximity to the target nerve. About 10% of the current flowing between the two surface electrodes is "picked up" by the lead at its receiving end and delivered to the nerve. This type of NP, known as the StimRouter^{TM} (98, 99, 101, 249),

is FDA-approved for pain mitigation (71) and is currently the subject of a multicenter clinical trial for the treatment of overactive bladder (186).

Electrode corrosion and tissue damage

The electrode-tissue interface impedance has both resistive and capacitive components. The resistive component of a current pulse is associated with charge being transferred across the interface. The capacitive component is associated with charge accumulating on either side of the interface. When a train of monophasic current pulses is delivered, if the charge per pulse and charge density are high, the interpulse interval may not allow enough time for the ionic changes at the electrode interface to reestablish an equilibrium between pulses (201). Irreversible electrochemical reactions may then occur, leading to electrode dissolution, a reduction in local pH in the tissues and tissue damage (2, 187).

The use of biphasic current pulses, in which the charge injected in the first phase (typically lasting 50-150 ms) is "pulled back out" in the second phase, greatly reduces irreversible reactions. This is called charge balancing. The function of the primary pulse is to excite the nerve; the function of the secondary pulse is to reverse the electrochemical processes that occurred during the primary pulse (201). To quote (264): "the reactions that occur during the first, cathodic, half of the pulse are double-layer charging, oxide reduction, 0_2 reduction, H_2 evolution, and H absorption. In the anodic half of the pulse, the reactions that occur are a reoxidation of the absorbed H, double-layer charging, oxide formation, metal corrosion, and O_2 evolution. The rates at which each of these reactions occur and the total time for their completion may vary considerably. This may result in many of these reactions occurring simultaneously".

The proportion of reactions that are irreversible increases with pulse duration and current (203). Generally, NPs are designed to deliver 100% charge balanced phases, but there is evidence that up to 50% charge imbalance may actually result in less tissue damage, presumably because the second, smaller, phase does not "pull out" charge lost to irreversible reactions (264).

Surface electrodes are usually large enough for corrosion to be negligible, but inflammation and damage can occur in the skin at the pulse amplitudes that are needed to activate muscle nerves. Implanted electrodes, especially those used for microstimulation, have small conductive surface areas at the nerve interface. The charge density can therefore be high and consequently, electrode dissolution and nerve damage can occur. Metals vary in the charge density and charge per pulse that result in dissolution. For example, platinum and certain stainless steel alloys tolerate high charge densities and are widely used in implanted electrodes. Charge density can be reduced by using a conductor with a coating of a rough material that presents a large surface area and also acts as a dielectric, such as sputtered iridium (64). Tissue damage may occur even in the absence of electrode deterioration (264). Detailed information and guidelines on the choice of conductors, and the safe limits of charge density, charge per pulse, and phase duration have been published (3,63,188,189, 194,263,329).

At the 40 pulses/s maximal pulse rates used in MNPs, metal dissolution is less of a problem than it is in cochlear implants, where pulse frequencies of up to several KHz have been used (236).

Motor NPs: Modes of operation

MNPs either deliver fixed sequences of stimulation for exercise and retraining purposes (therapeutic electrical stimulation: TES), or stimulation triggered by biomechanical events or by the user to replace or augment muscle contractions in exercise training, or in functional tasks such as walking, breathing, and grasp-release (functional electrical stimulation: FES).

TES stimulators have been widely used by physical and occupational therapists since the 1970s. They are surface MNPs (Fig. 1A). For many years, the standard TES device to be found in clinics was the Medtronic Respond II (Fig. 3A), a two-channel stimulator that delivered trains of stimulus pulses in cyclical patterns that could be selected by the therapist or patient. The Respond was discontinued when Medtronic withdrew from the surface NP sector in the 1980s. It was supplanted by the Empi 300PV. This was in turn discontinued in 2015. Currently, muscle stimulators suitable for TES include the Electro Med Supply EMS7600, RS Medical RS4i, and Therapeutic Alliances SpectraSTIM E3. TES has been used for both upper and lower extremity TES (159).

The most widely used FES devices are the foot-drop stimulator, the grasp-release stimulator, and the phrenic pacer (see the following text). FES has also been used for many years in specialized rehabilitation centers to activate paralyzed leg muscles, enabling exercise on bicycle ergometers (234, 235). Intensive exercise over extended periods has been shown to counteract muscle atrophy, improve local blood circulation, increase range of motion, and reduce muscle spasticity. The term "FES cycling" is used by the manufacturers to describe such systems (musclepower.com, restorative-therapies.com).

EMG triggering

The electromyogram (EMG) recorded from a muscle under volitional control has been used as a means of controlling FES of a separate, paralyzed muscle (111, 112, 131, 193, 315, 324). Another approach is to sample the EMG of a weakly contracting muscle through a pair of surface electrodes. When a pre-set threshold is reached, stimulation is delivered through the same electrodes. This method was first used in the Automove (117). Its successor, the Neuromove (Fig. 3B), is commercially available and is used in rehabilitation centers to strengthen paretic muscles after stroke and spinal cord injury (93, 159). Another method is to boost the contraction of a weak muscle by recording the EMG and stimulating at the

same time rather than sequentially. A pair of recording electrodes is attached at right angles and halfway between a pair of stimulating electrodes (132, 298). This orthogonal orientation and the use of stimulus-blocking amplifiers minimizes stimulus artifacts in the EMG. When the recording and stimulating electrodes are implanted, the stimuli and therefore the EMG artifacts are smaller (131, 176).

Types of Motor NPs

Lower limb MNPs: Transcutaneous peripheral nerve and muscle stimulators

The first and most successful FES device was designed to correct foot-drop in people with hemiparesis by delivering trains of stimuli to the common peroneal nerve through surface electrodes (174). A switch built into an insole was used to detect the moment the user's heel began to lift, at the onset of the swing phase of locomotion. This triggered stimulation, activating the foot dorsiflexor muscles extensor digitorum longus and tibialis anterior. A commercial version of this device, the functional electrical peroneal orthosis (FEPO), was developed by a group in Ljubljana in the mid-1970s and marketed in Europe by a company in Germany (165) (Fig. 2A). Users found it tricky to connect leads from the stimulator through the elastic knee stocking to press-studs on the electrodes inside the garment. The leads, connectors and the insole switch were flimsy and had a high failure rate. The button pad electrodes were small, resulting in a high current density that could be painful.

In the 1990s and early 2000s, more convenient and robust foot-drop stimulators have been developed and used by over 10,000 people with hemiplegia due to stroke, traumatic brain injury, multiple sclerosis, and spinal cord injury (SCI). Four devices, in the form of electrode-containing cuffs worn below the knee, have been commercialized: the Innovative Neurotronics WalkAide (141) (Fig. 2B), the Bioness L300 (33) (Fig. 2C), the Odstock Dropped Foot Stimulator ODFS (218), and the Otto Bock MyGait (221). The L300, ODFS, and MyGait have underheel sensors wirelessly linked to an EPG in the cuff to trigger stimulation. The Walkaide has a tilt sensor built into the cuff, which is used to trigger stimulation, replacing the underheel sensor and allowing users to walk barefoot (66). This was exclusive to the Walkaide until the patent expired in 2015 (282). The Bioness L300Go now uses this method too (Fig. 2D). Standard physical therapy stimulators equipped with underheel sensors have also been used as foot-drop stimulators (e.g., the Empi 300PV, no longer commercially available). Sales of the MyGait appear to have been discontinued, at least in the UK.

A 6-channel FES stimulator, the Parastep, was developed in the 1990s (142). It is used with a walker and controlled by hand-switches. The metabolic costs are high (97, 157, 280). To quote one study: "In spite of its ease of operation and good cosmetic acceptance, the Parastep approach has very limited applications for mobility in daily life, because of its modest performance associated with high metabolic cost and cardiovascular strain. However, it can be proposed as a resource to keep physical and psychological fitness in patients with SCI" (47). The Parastep is available through the W.A.L.K. Foundation (sigmedics.com) and some Veterans Administration and private clinics (Maltezos, personal communication).

Clinical studies have compared the efficacy of foot-drop FES stimulators and conventional ankle-foot orthoses (AFOs) (50, 262, 274, 295, 309). In two large randomized controlled trials involving the Bioness L300 (158) and the Innovative

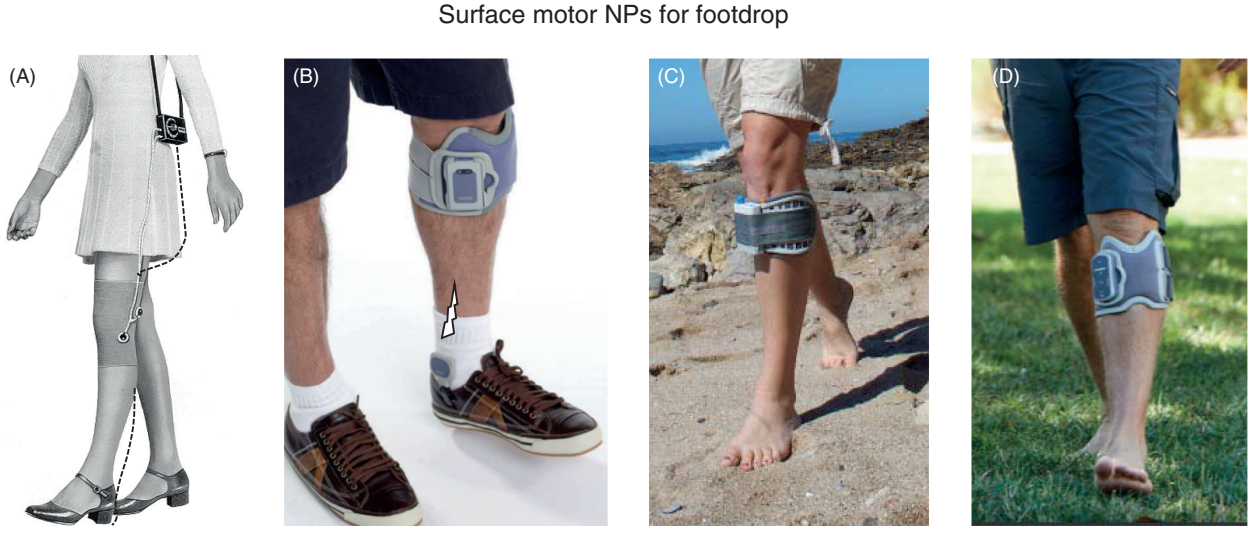

Figure 2 Four surface foot-drop stimulators that activate the common peroneal nerve to lift the foot in the swing phase of the locomotor step cycle. (A) The Functional Electrical Peroneal Orthosis (FEPO), commercialized in Europe in the 1970s. (B) The Bioness L300. (C) The Innovative Neurotronics Walkaide. (D) The Bioness L300Go. The FEPO and L300 had underheel switches wirelessly linked to an EPG in a cuff attached below the knee. When the underheel force dropped at the onset of the swing phase, a signal from the switch assembly triggered the EPG to stimulate the nerve via electrodes in the cuff. The Walkaide and Bioness L300Go have a tilt sensor built into the cuff, which is used to trigger stimulation, replacing the underheel switch and allowing users to walk barefoot.

Neurotronics Walkaide (31), no significant differences were found between the FES and AFO groups in a variety of motor function tests. However, satisfaction was significantly higher in the FES group than in the AFO group. It was concluded that "the development of a validated measure of user satisfaction is important to adequately capture the factors that lead to long-term compliance and the subjective experience of the individual with drop foot from stroke." (158). Unfortunately, the lack of a clear advantage of foot-drop stimulators over AFOs meant that there were insufficient grounds for reimbursement of these devices.

The 2016 Evidence-based Review of Stroke Rehabilitation metastudy concluded that "There is level 1a and level 2 evidence that FES may improve gait, balance, and range of motion" (91). The 2010 Spinal Cord Injury Rehabilitation Evidence metastudy concluded that "FES-assisted walking can enable walking or enhance walking speed in incomplete SCI or complete (T4-T11) SCI. Regular use of FES in gait training or activities of daily living can lead to improvement in walking even when the stimulator is not in use." (168).

Lower limb MNPs: Implantable peripheral nerve and intramuscular stimulators

Within a year of Liberson's invention of the switch-triggered foot-drop stimulator, work began on an implantable version, the Medtronic/Rancho Los Amigos Hospital Neuromuscular Assist Device (61). An underheel sensor wirelessly triggered an external stimulator worn on the user's belt. This delivered power and stimulus commands to an implanted receiver via an antenna taped to the skin. The receiver delivered stimuli to the common peroneal nerve via electrodes that ran subcutaneously down the leg, terminating in a nerve cuff distal to the knee (192). The developers implanted 22 people with hemiparesis with the device and in 1972, an expanded multicenter trial involving 37 people was initiated. The concluding report on this work by the Committee on Prosthetics Research and Development for the National Research Council was generally favorable, with 46 of the 59 implants deemed successful, 7 failing because of equipment problems and 6 failing due to nerve damage caused by the cuff (61). Low enrolment and poor device reliability were identified as the main problems encountered. In follow-ups, it was reported that the system continued to be used by 25 of 31 recipients for at least 7 years (192, 285, 319). In spite of positive assessments by participating clinical centers, and a favorable forecast of success by the reporting committee, Medtronic decided not to pursue commercialization of the device.

Implantable foot-drop stimulators were revisited in the early 2000s in Europe: the Finetech STIMuSTEP (www.finetech-medical.co.uk) and the Neurodan ActiGait (www.neurodan.com). Both devices were wirelessly triggered with the use of underheel sensors. Ten people with foot-drop were implanted with the STIMuSTEP (150, 160) and 21 with the ActiGait (52, 184, 265). Nearly all participants showed significant improvements in gait (80). Technical problems occurred, but were resolved at follow-up (53). Nonetheless, in the face of regulatory and other hurdles, the commercial development of both devices was eventually discontinued.

The first fully implanted MNP, the Neurostep, was tested clinically in a hemiparetic man with foot-drop some years ago (118, 121, 133-135). Cutaneous signals from the heel of the foot were used to detect heel-off and trigger stimulation of the common peroneal nerve. As in the aforementioned cases, commercialization of the Neurostep has also foundered. This all-too-common outcome in the implantable MNP field is discussed in the Barriers section below.

Implantable MNPs that stimulate multiple leg muscles have been developed and tested clinically (1, 67, 124, 181, 227, 269). Encouraging results were obtained in clinical trials, in the restoration of posture and standing (18) and the avoidance of pressure ulcers (39, 92, 323).

Upper limb MNPs: Transcutaneous peripheral nerve and muscle stimulators

Up to 60% of the 9 million people living with the aftereffects of stroke and SCI in North America find it difficult or impossible to perform activities of daily life because of poor upper limb function (82, 85, 305). Problems include difficulty extending the forearm, hand and digits, difficulty grasping and releasing objects and spastic hypertonus. Upper limb function is at the top of the "wish-list" of stroke survivors and people with tetraplegia due to spinal cord injury (14, 25, 26). Meaningful recovery of upper limb function includes the ability to use the paretic limb in home and community activities (321).

Unlike the lower limb, where a viable and cosmetically satisfactory alternative to FES exists in the form of splints, mechanical devices that assist in upper limb activities of daily life tend to be cumbersome and cosmetically unappealing. The use of electrical stimulation for upper limb rehabilitation commenced in the 1960s (258, 314). In the late 1970s, a TES device comprising a stimulator and a hinged splint containing surface electrodes was used in a daily exercise program at the Rancho Los Amigos Rehabilitation Hospital (22, 318). The first commercial upper limb stimulator was the EMG-triggered Automove, now sold as the Neuromove (Fig. 3B, see *EMG-triggering* above). Several studies have reported improvements in unassisted voluntary function in participants with sub-acute and chronic stroke following upper limb retraining with the Neuromove (56, 59, 68, 93, 122).

In the 1990s, two grasp-release FES devices were developed: the Handmaster and the Bionic Glove. Both were originally designed for SCI users but were later modified for people with stroke. The Handmaster, renamed the Bioness H200 in 2005, is a hinged plastic wrist splint with built-in electrodes (216). Originally, the splint was connected to a stimulator by a cable (Fig. 3C). In 2014, the stimulator was built into the splint and triggered by a wireless push-button. Several studies were performed in which the Handmaster was used in daily exercise programs in people with stroke and SCI (8-11, 279).

Figure 3 Four surface stimulators that activate muscles in the forearm and hand. (A) The Medtronic Respond physiotherapy stimulator activating the wrist and finger extensors. Preset trains of stimulus pulses were triggered by activating a hand-held push-button. Numerous therapeutic stimulators based on this design are commercially available. (B) The EMG-triggered Neuromove. Weak voluntary contractions are detected via a pair of surface electrodes and this triggers a preset period of stimulation through a pair of electrodes placed orthogonally to the electromyogram electrodes. (C) The Bioness H200. This device comprises a flexible splint with inbuilt electrodes. Trains of stimuli eliciting hand opening and grasp are triggered via a radiofrequency push-button controller. (D) The Rehabtronics ReGrasp comprises a wristlet garment with inbuilt stimulator/receiver and electrodes. A wireless earpiece detects voluntary head movements and transmits control signals to the wristlet, by which means the user can trigger hand opening or grasp.

The results were generally favorable, showing statistically significant improvements in upper limb activities of daily life after some weeks of use. A recent review concluded that the splint "prevents the use of a tenodesis grip. Hence, a robust and versatile upper limb FES device that can be used by a wider group of people is required" (311).

The Bionic Glove had metal-mesh panels, a wrist displacement sensor and a stimulator built into a fingerless garment (251, 254). When this was donned, the mesh panels made contact with self-adhesive electrodes previously placed on the forearm and hand. Voluntary wrist extension and flexion triggered stimulation that augmented the user's tenodesis grasp and release. In 9 people with C6-7 SCI, grasp force increased fourfold and activities of daily life improved significantly (251). In an independent study in 12 people with C5-7 SCI, after 6 months of using the Bionic Glove in activities of daily life, improvements were observed in voluntary hand function in the absence of stimulation (242).

The Bionic Glove was superseded by a soft wristlet triggered by a wireless earpiece that detected tooth-clicks (248). This device was used in studies of FES-assisted training on a telerehabilitation workstation in people with chronic tetraplegia (162) and chronic hemiplegia (49). In the latest configuration, the Rehabtronics ReGrasp, the earpiece detects head-nods (Fig. 3D). The ReGrasp has received FDA and EC clearance for sale in the United States and Europe.

Multichannel upper-limb FES with surface electrodes has been tested in people with C3-7 tetraplegia (244, 245). The stimulator activates arm muscles in a proximal to distal sequence, enabling reach and grasp-release. The motor points of proximal muscles can move several centimeters under the skin during flexion and extension, so it is a challenge to

control these movements accurately. Nevertheless, encouraging results have been reported (149, 179). The device is commercially available for use in Canada: http://www.myndtec.com/myndmove.

Upper limb MNPs: Implantable peripheral nerve and intramuscular stimulators

An implanted multichannel stimulator to restore upper limb movements after SCI was developed in the 1980s at Case Western Reserve University (224). The system was of the type shown in Figure 1D, comprising an implanted pulse generator with leads that terminated in button electrodes that were sewn to the epimysium of muscles in the forearm and hand. External shoulder or wrist movement sensors were used to provide the recipients with voluntary control over muscle stimulation. The external controller transmitted commands by inductive coupling through a coil taped to the skin. Muscles were stimulated in specific combinations to produce different types of hand movement. The device was approved by the FDA in 1997 and commercialized as the "Freehand System," about 200 of which were implanted in people with C4-C5 tetraplegia. Though the technology was highly advanced and many recipients benefited significantly (225), the device was discontinued in 2002 (see Barriers section).

The most recent developments in this area have been studies in which microelectrode arrays implanted in the motor cortex of monkeys (54, 81) and humans (40) were used to control stimulation of paralyzed muscles. In the most recent study, muscle stimulation was delivered through electrodes inserted percutaneously into upper limb muscles of a man with tetraplegia (Fig. 4). This enabled him voluntarily to reach out with his weight-supported arm to drink a mug of coffee and feed himself (5). Neural recordings from currently available microelectrode arrays (148, 217) slowly degrade over months and years (229, 230, 278, 325). In a retrospective study of 78 implants in 27 monkeys, useable recordings were obtained for a mean of 387 days (27). iBCI arrays would have to last for decades for this approach to be adopted clinically. Dielectric and bioactive coatings may provide the solution (84, 164). Another possibility is to use electrocorticogram (ECoG) electrodes implanted epidurally or subdurally (41, 90, 138, 173, 310, 312, 317). It remains to be seen whether ECoG signals can provide enough information to control multiple arm muscles in voluntary tasks.

Simpler one- or two-channel implantable upper limb MNPs include the Finetech STIMuGRIP (281) and the StimRouter (100). In the STIMuGRIP, an internal pulse generator was implanted, with the ends of two pairs of epimysial leads secured to motor points of muscles in the forearm. An external controller strapped to the forearm over the internal pulse generator provided energy and commands. An accelerometer in the external controller detected specific voluntary movements of the forearm, which the users made to trigger wrist extension and hand opening. Two hemiplegic people were implanted in a pilot study (88). No further development or clinical testing of this device has occurred.

In the StimRouter system (Fig. 1C), nerve cuffs were implanted on three nerves in the forearm controlling hand opening and grasp. The leads from the nerve cuffs terminated in conductive pick-up ends under the skin proximal to the wrist. The users wore a wristlet containing an external controller and pad electrodes. Pulse trains were delivered by the controller via the pad electrodes through the skin. Some of the current was picked up by the leads and delivered to the nerves. Hand opening, grasp, and release were triggered sequentially with voluntary toothclicks, detected by the wireless earpiece described above. A tetraplegic man was implanted with this system in 2008 and used it successfully in activities of daily life for several years (101). In 2012 two tetraplegic women were implanted with the same system. In both cases, the leads that activated thumb opposition failed within a day or two of implantation, so no further implants were performed. However, the enhancement in hand opening and grasp was sufficient for one of the women to continue using her system regularly to the present day. In 2015, the StimRouter received FDA clearance for chronic pain control (70, 71, 186) and is currently the subject of two multicenter trials for the treatment of overactive bladder and shoulder subluxation (https://clinicaltrials.gov: NCT02873312 and NCT03093935).

Respiratory MNPs

Electrical stimulation of the phrenic nerve to restore breathing was proposed in the 18th Century and first tested in 1819 (65). In the mid-1960s, Glenn and colleagues reported the first clinical trials of an implanted phrenic nerve stimulator controlled by an external radio-frequency controller (307). The system was refined and commercialized by Avery Laboratories, Inc. (79, 109) and received FDA pre-market approval in 1987. According to the Avery Biomedical Devices website, over 2000 patients have been implanted with the device in over 40 countries. Phrenic nerve stimulators were also commercialized in Austria (MedImplant, Vienna) (108, 297) and Finland (Atrostim: atrotech.com) (20, 289). Multiple electrodes were attached to each phrenic nerve in these devices, allowing sequential stimulation of different parts of the diaphragm. As mentioned above in "Activating nerves and muscles electrically," distributed stimulation enhances force generation and reduces muscle fatigue (255). Numerous studies have appeared confirming the safety and functionality of phrenic nerve stimulators in both conditioning and pacing the diaphragm (170). A study in 32 patients receiving mechanical ventilation and 32 receiving phrenic nerve stimulation found that in the phrenic pacing group, respiratory infections were more than halved, quality of speech and quality of life were significantly better and overall costs were lower after 1 year. An interesting video clip shows the difficulty of surgically tethering a nerve cuff to the phrenic nerve adjacent to the beating heart: https://youtu.be/gBwIQUmUKIQ. A nerve

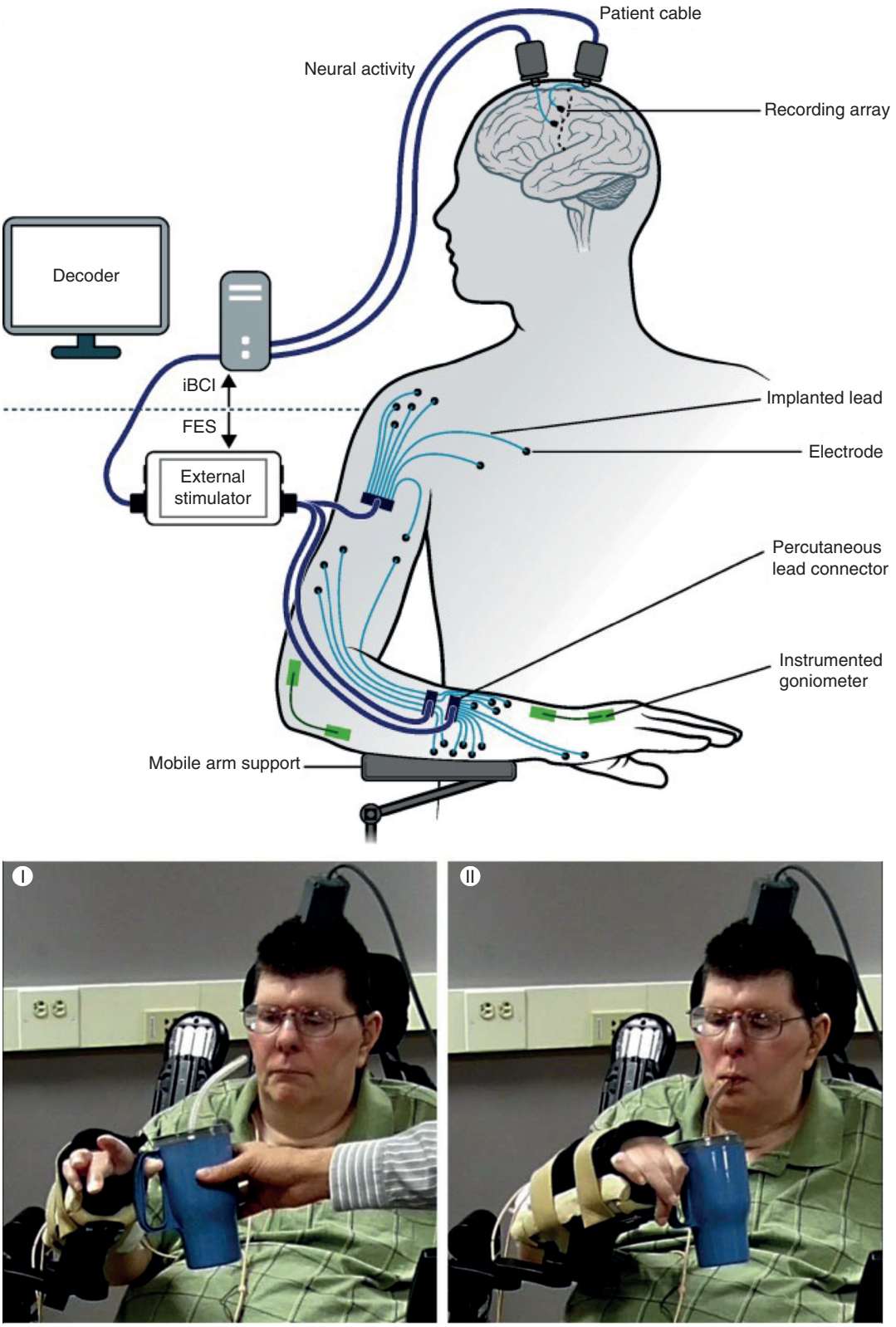

Figure 4 Proximal and distal muscle activation in which signals from a microelectrode array implanted in the motor cortex of a tetraplegic man were used to control stimulation through electrodes inserted percutaneously into his upper limb. This enabled him voluntarily to reach out with his weight-supported arm to drink a mug of coffee and feed himself. Reproduced with permission from (5).

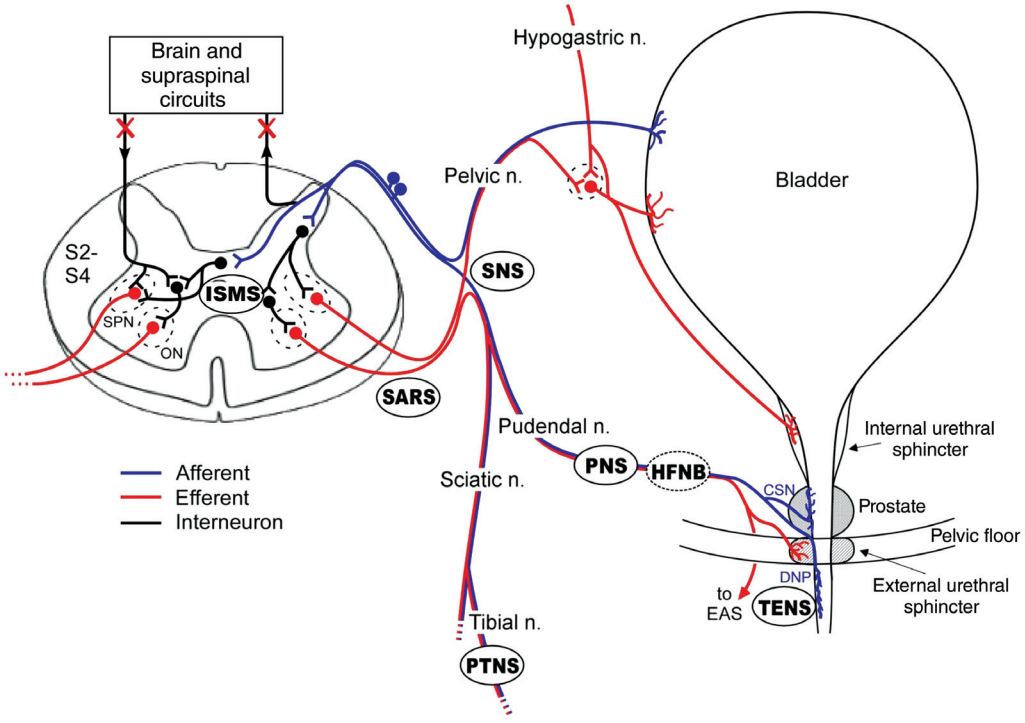

Figure 5 Sacral spinal cord targets (segments S2-S4) for electrical stimulation to improve bladder function. SNS, sacral nerve stimulation; SARS, sacral anterior root stimulation; ISMS, intraspinal microstimulation; PNS, pudendal nerve stimulation; PTNS, percutaneous tibial nerve stimulation; TENS, transcutaneous electrical nerve stimulation; HFNB, high-frequency stimulation eliciting nerve block (HFNB); SPN, sacral parasympathetic nucleus (activates bladder contractions); ON, Onuf's nucleus; CSN, cranial sensory neuron; DNP, dorsal nerve of the penis (DNP). Reproduced with permission from (190).

cuff electrode based on a zip-tie, developed for the StimRouter system, provides easier placement and sizing to nerve diameter, but it has not been commercialized (101, 161).

Two alternative diaphragm-pacing systems have been developed in the last two decades. The first is the NeuRx diaphragm pacer (4, 73, 219, 286) in which laparoscopically placed, percutaneous intramuscular electrodes are used to stimulate the diaphragm. The device has FDA Humanitarian Device Exemption approval for conditioning the diaphragm in people with spinal cord injury (SCI) and amyotrophic lateral sclerosis (ALS) (220). There are conflicting reports on the long-term efficacy and safety of this device (72,170,220,246). The second involves phrenic nerve stimulation through a multielectrode catheter introduced into the subclavian vein and superior vena cava (136, 260). The electrodes are tested to determine the combinations that elicit the strongest diaphragmatic responses. The device has FDA approval as an investigational device and is not commercially available at the time of writing.

MNPs for bladder control

The neural control of continence and voiding of the urinary bladder in humans involves all levels of the central nervous system. Sensory signals from stretch receptors in the bladder wall ascend to the pontine micturition center (PMC) and cerebral cortex (Fig. 5) (190). When the bladder is distended beyond a threshold volume, descending drive from the brain and PMC to the sacral parasympathetic nucleus (SPN) activates efferent neurons that elicit bladder contractions. At the same time, Onuf's nucleus, whose efferents otherwise maintain continence by activating the external urethral sphincter, is inhibited by neurons in the dorsal gray commissure of the spinal cord. The reciprocal activation of the bladder and inhibition of the external urethral sphincter enables voiding. This complex system is disrupted in a variety of disorders, including SCI, stroke, amyotrophic lateral sclerosis, peripheral neuropathies, Parkinson's disease, and multiple sclerosis.

In the 1980s, Tanagho and Schmidt showed in a series of animal experiments that low-frequency, low-amplitude stimulation of the sacral nerve improved continence by maintaining sphincter contraction, without concomitant bladder contraction (290-292). In fact, bladder contractions were reflexly *inhibited* by the sphincter contractions, further facilitating continence. Minimally invasive methods of accessing the sacral nerves through the sacral foramina were then developed (266). Based on this work, the Interstim® sacral nerve stimulator (SNS: Figure 5) was commercialized by Medtronic Inc. (Minneapolis, MN, USA) (InterStim) and approved by the FDA in 1997 for urge incontinence and in 1999 for urinary retention of neurological origin. The mechanism in the

latter case, which logically should be opposite to that for incontinence, is poorly understood, and possibly attributable to neuromodulation (see the following text).

The Interstim device is also used off-label to treat overactive bladder. Randomized controlled trials comparing Interstim SNS with standard medical therapy have shown that voiding frequency and incontinence improved more in the SNS groups, as did symptom bother and interference scores (120, 277). The American Urological Association guidelines support SNS in "a carefully selected patient population characterized by severe refractory overactive bladder symptoms or patients who are not candidates for second-line therapy and are willing to undergo a surgical procedure." These devices are expensive and about 25% of implants result in adverse events requiring hospitalization (30). Surgical revisions or explantations are fairly frequent (223, 276).

Many people with SCI suffer from bladder-sphincter dyssynergia. In the absence of descending drive from the PMC, during spontaneous bladder contractions, the external urethral sphincter also reflexly contracts instead of relaxing, thus preventing voiding. Transecting the posterior spinal roots abolishes the reflex contractions (44, 125). Electrical stimulation of the sacral anterior roots activates parasympathetic preganglionic axons from SPN that elicit bladder contractions but unfortunately it also activates motor axons innerving the sphincter. However, it was found that after a brief train of stimuli, the sphincter relaxes faster than the bladder, allowing a few seconds of voiding. When this is repeated numerous times, satisfactory voiding can be achieved (46, 293). The Brindley-Finetech Sacral Anterior Root Stimulator (SARS) is based on this method (Finetech Medical Ltd., Welwyn Garden City, UK). It has been implanted in over 2,500 people (261), the majority of whom achieved residual bladder volumes of less than 30 ml, which freed them from catheter usage, reducing their incidence of urinary tract infections (183, 308).

Another experimental approach is to stimulate the pudendal nerve (Fig. 5 PNS). Motor axons in this nerve activate the external urethral sphincter, but the nerve also contains sensory axons from the pelvic floor, urethra, and external genitalia. The sensory input can either reflexly inhibit or facilitate bladder contractions, (190). Depending on stimulus parameters, selective stimulation of the sensory and motor branches of the pudendal nerve has been found either to inhibit the sphincter and excite the bladder for voiding, or to inhibit the bladder and excite the sphincter to promote continence (37, 38, 172, 190, 327, 328). High-frequency blockade of the pudendal nerve to relax the sphincter is another promising line of investigation (32, 36, 104, 105, 156, 287, 288) (Fig. 5 HFNB).

Finally, posterior tibial nerve stimulation (PTNS) above the ankle, either with a TENS stimulator or a percutaneous needle, has been shown to reduce the symptoms of overactive bladder (231,232). The posterior tibial nerve contains sensory and motor axons of the L4-S3 spinal roots, the same spinal cord segments that control the bladder and urethral sphincters. The main action of PTNS on overactive bladder can take weeks to develop (231). For this reason, the effect has been labelled "neuromodulatory," with the assumption that PTNS causes slow changes in neurotransmitter concentrations (see below).

Researchers at the Vrije University in Amsterdam have implanted an Uroplasty Urgent-SQ PTNS stimulator in eight people (302, 303, 306), five of whom experienced improvements in overactive bladder symptoms and quality of life. Three were still using their devices regularly 9 years post-implantation (143). An Israeli device, the Bluewind RENOVA, is a microstimulator that is implanted percutaneously near the posterior tibial nerve with a cannula. A pilot study has shown promising results (123,304). Finally, as mentioned above, a PTNS based on the StimRouter is in clinical trials for overactive bladder.

The development of these user-controlled implantable devices was motivated by the idea that if clients were able to deliver PTNS more frequently in their home environment, they would be able to control their OAB symptoms better. Furthermore, since there is some evidence of immediate inhibition of detrusor activity by PTNS (12, 267), users might be able to apply PTNS at the first onset of an OAB event, thus reducing urgency and leaks (though in a small study in multiple sclerosis patients, immediate inhibition of bladder contractions was not observed (89)).

Epidural and intraspinal stimulation and intraspinal microstimulation (ISMS)

Epidural stimulation of the spinal cord via electrodes placed on the dorsal dura mater, originally developed to treat chronic pain (211, 271, 273), has been studied as a means of augmenting residual locomotor function after SCI (17, 55, 74, 107, 119, 129, 259). The method was originally called dorsal column stimulation as it was thought that axons in the dorsal columns of the spinal cord were the structures primarily activated. It was assumed that with increasing amplitudes, epidural stimulation also activated interneurons in the spinal cord gray matter. Subsequent studies showed that in fact epidural spinal cord stimulation activates axons in dorsal root filaments at lower amplitudes than axons in the dorsal columns or interneuronal cell bodies in the spinal cord (167, 256, 257). The resulting sensory input has been posited to increase the general level of excitability of spinal locomotor circuits (210).

Epidural stimulation has generally been delivered as a continuous train of pulses applied through an array of electrode terminals spanning several segments of the spinal cord. In a series of recent, elegant studies in rats, monkeys and humans, Courtine and colleagues have found that spatiotemporal epidural stimulation alternating between flexion and extension "hot-spots" in the spinal cord (326) is more effective in generating locomotor movements in rats and monkeys with SCI than continuous stimulation (54,199,320). This may be because epidural stimulation antidromically blocks proprioceptive input and this would not occur in the off-phases of

spatially alternating stimulation. In the group's latest research, spatiotemporal epidural stimulation enabled robotic-assisted walking in nonambulatory people with complete or partial chronic SCI (316).

Epidural stimulation has also been used to reduce spasticity (239), but the long-term efficacy and cost-effectiveness of this approach has been questioned (195). Recent reports indicate that locomotor training facilitated by epidural stimulation results in other medical benefits including bladder, bowel and sexual function as well as overall bodily composition (139, 296).

In the last few years transcutaneous electrical stimulation of the spinal roots or spinal cord with large surface electrodes and high amplitude current pulses has been shown to facilitate both locomotion and upper limb function in people with tetraplegia (6, 96, 197).

Over a hundred years ago, electrical stimulation of the sacral spinal cord was shown to elicit bladder contractions in anesthetized cats (284). Seventy years later, intraspinal stimulation was explored in cats and humans as a means of restoring bladder control after SCI (213, 214). Pairs of insulated platinum-iridium wires (0.406 mm diameter, 0.5 mm bared tips) were implanted in the sacral spinal cord (94). Stimulation in 5 of 10 cats with chronically transected spinal cords elicited voiding. Coactivation of the urethral sphincter with the bladder was a problem, but repeated bursts of post-stimulus voiding could be used to empty the bladder (147).

In all, 27 people with SCI were implanted with intraspinal electrodes (215). Stimulation was remotely controlled with a radiofrequency transmitter linked to an implanted receiver-stimulator. Three of four recipients implanted in the first study showed good voiding (214). Poststimulus voiding was unsuccessful in the two male participants, so partial transurethral sphincterotomies were performed, improving voiding. Overall 16 of the 27 recipients experienced good voiding with low residual volumes, reductions in urinary tract infections, increases in bladder capacity and freedom from catheterization (215). Some autonomic and motor side effects were reported (215). The program was eventually discontinued, presumably because of the invasive nature of the intraspinal electrodes, the need for additional surgery to overcome bladder-sphincter dyssynergia and the 40% failure rate (215).

The conductive surface areas of the tips of Nashold and Friedman's intraspinal electrodes were 50 to 300 times larger than those of the electrodes more recently used in intraspinal *micro*stimulation (ISMS) studies (103). In the more recent experiments in cats, pulse trains were delivered via ISMS electrodes to the sacral parasympathetic nucleus to produce bladder contractions (114, 330) and to the dorsal gray commissure to inhibit Onuf's nucleus and thereby relax the external urethral sphincter (35, 102, 114, 238). This sometimes increased bladder pressure while decreasing sphincter pressure, as was desired, but it rarely resulted in complete voiding. In the future, it may be possible to develop multicontact electrode arrays that allow the selection of specific stimulation sites that activate the bladder and inhibit the sphincter to produce reliable voiding.

ISMS through microwires implanted in the lumbosacral spinal cord in cats has been shown to activate single muscles or groups of synergistic muscles (205-208). Technical difficulties encountered in ISMS implants include inserting electrodes into specific motoneuron pools, maintaining these locations and tissue damage over time (115). After some weeks, the movements elicited by ISMS may change from the desired synergies to co-contraction of several muscles (200). Evidence of inflammation and neuronal damage around implanted microwires has been reported (27, 240).

A direct comparison between epidural stimulation (on both dorsal and ventral aspects of the spinal cord), dorsal subdural stimulation, and ISMS has been performed in anesthetized monkeys (270). Subdural stimulation was more selective than either epidural stimulation or ISMS. Ventral epidural stimulation elicited direct responses in motoneurons, whereas dorsal epidural stimulation and ISMS elicited more complex responses attributable to the activation of afferent axons, descending axons and possibly interneurons, as previous studies have suggested (106, 256). ISMS and epidural stimulation coactivated several muscles at low thresholds, and these muscles were not necessarily synergistic. The animals in this study were anesthetized and, unlike in SCI, the descending pathways to motoneurons were intact. The authors argued that in their experience, responses to ISMS in awake animals were generally similar in terms of thresholds and evoked movements to those in anesthetized animals.

As there have been no human implants of ISMS systems for controlling movement, it is too early to decide whether the presumed advantage of ISMS over epidural stimulation (greater selectivity of muscle activation) outweighs the disadvantages (invasiveness, risk of infection, electrode migration, tissue damage).

It has been proposed that residual voluntary movement could be boosted by low-intensity ISMS that causes a diffuse increase in excitation of spinal neuronal networks (252, 253). This is similar to the mechanism proposed above for epidural stimulation. In a recent study in monkeys in which one hand was paralyzed by a temporary blockade of the motor cortex, ISMS controlled with the use of recorded activity of premotor cortical neurons, enabled the animals to move the hand (331).

Deep brain stimulation

Deep brain stimulation (DBS), pioneered in the 1980s by Benabid and colleagues in France (29) has become a widely-adopted surgical treatment for Parkinson's disease, essential tremor, dystonia, and a number of nonmotor neurological disorders (19). High-frequency stimulation (~130 pulses/sec) of the subthalamic nucleus (STN) and neighboring basal ganglia targets through multi-channel electrodes surgically lowered into the brain can reduce or abolish essential tremor and the tremor and rigidity of Parkinson's disease. The inhibition of these involuntary motor outputs allows controlled, voluntary

movement to take place. Thus, although DBS acts by inhibiting certain components of movement, nonetheless, it can be considered to have a motor neuroprosthetic action according to the definition proposed earlier in this article.

The mechanisms by which the beneficial effects of DBS occur remain controversial, in spite of over 30 years of research. A large body of research indicates that DBS disrupts aberrant neuronal firing patterns in the subthalamic nucleus and globus pallidus internus (322). This could be the result of entrainment of overactive, randomly firing STN neurons to the stimulus frequency, activation of incoming inhibitory axons, or antidromic suppression of descending cortical drive to STN neurons (15, 196, 322). Spectacular improvements in tremor and rigidity often occur within seconds of stimulation onset, but there is also evidence for more subtle, slower-onset, neuromodulatory effects, and structural reorganization of the brain (neuroplasticity) (19, 130). DBS stimulators have been implanted in over 100,000 people worldwide. Currently three manufacturers in the United States dominate the world market: Medtronic, St. Jude Medical and Boston Scientific (35, 102, 114, 238, 330).

Carry-over and therapeutic effects, neuromodulation

In about a quarter of cases, after a session of TES and FES in people with stroke or SCI, voluntary control of the affected muscles may improve for several hours (16,272,313). Longer-term improvements occur when electrical stimulation is used to augment voluntary effort (56-58, 69, 163, 210, 222, 245). The phenomenon of carry-over has been reviewed elsewhere (91, 159), the main conclusions being:

1. Regular application of TES or FES over several weeks can improve the strength and control of voluntary movements in people with paresis due to stroke or SCI.

2. There is conflicting evidence regarding whether FES results in greater improvements than TES.

3. If FES or TES are applied during functional tasks involving voluntary effort, this leads to greater improvements than when applied in the absence of voluntary effort.

Several mechanisms have been implicated in improving voluntary control after FES or TES. (i) Regular sessions of electrical stimulation have long been known to increase muscle mass and contractile force. Fatigue resistance increases due to conversion of fast-twitch fast-fatiguing glycolytic type II muscle fibers to slow-twitch fatigue-resistant oxidative type I muscle fibers (283). (ii) Muscle stimulation reduces edema and improves blood flow in muscle and skin. (iii) Within the CNS, Hebbian plasticity has been implicated when cortical neurons are activated during voluntary effort and receive ascending input elicited by electrical stimulation (87). For example, after common peroneal nerve stimulation, foot dorsiflexion responses to transcranial magnetic stimulation are enhanced (154, 155). Changes in the brain after muscle stimulation have been detected in imaging studies (159). 4) Spastic hypertonus that impedes voluntary movement is reduced after FES and TES (178).

In contrast to carry-over effects, which last up to a few hours, in some NP applications, long-lasting beneficial effects develop slowly, over days or weeks, and may become permanent. Notable examples include sacral nerve and posterior tibial nerve stimulation for bladder control (23, 204, 301) spinal cord and peripheral nerve stimulation for chronic pain control (70, 268) and deep brain stimulation in Parkinson's disease, essential tremor and other neurological disorders (83,130,171). The onset latencies of the effects are of the same order as those observed in CNS responses to the release or application of molecular neuromodulators such as dopamine, serotonin, histamine, and norepinephrine. Consequently, the term neuromodulation has been applied to such NP effects. In addition to the release of neuromodulators, there is evidence that electrically mediated neuromodulation results in neuronal plasticity, the formation of new functional neuronal networks that develop weeks and months after stroke, SCI and limb amputation (198).

Barriers: Regulatory costs and reimbursement

TES stimulators such as the EMS7600 have become inexpensive consumer products, and are widely used by the public as well as in clinics. FES devices are much more expensive, because they incorporate sensors and control logic, they are designed to be wearable in daily life, and they are subjected to more stringent regulatory testing. Over the years, reimbursement has been provided for foot-drop stimulators in Yugoslavia (166), Denmark (Dr. Benny Klemar, personal communication), and the United Kingdom (294). In the 1980s, the USA Centers of Medicare and Medicaide Services (CMS) denied reimbursement for neuromuscular stimulators to treat neurological disorders, even though reimbursement was approved for the treatment of chronic back pain, which is a neuromuscular disorder. In 2006, CMS extended coverage to the Parastep neuromuscular stimulator for people with SCI who met certain restricted clinical criteria (62). The cost and limited coverage of FES devices has been a crucial barrier to the widespread adoption of MNPs (116).

It is a challenge to commercialize complex implantable NPs such as the Neurocontrol/Freehand upper limb FES system, because they have a relatively small market and so the income from sales is far less than the expenses associated with development, manufacturing and maintenance (226). In an interesting attempt to overcome this "valley of death," the nonprofit "Institute for Functional Restoration" was formed at Case Western University "to support technology transfer of devices that "lack the economics to warrant a traditional technology transfer model." The aim of the institute is "to develop the products and distribution channels, with the mission of full

commercial deployment if a for-profit solution is not found" (http://casemed.case.edu/ifr/). This initiative could provide a model for so-called orphan biomedical devices in the future.

Concluding Remarks

Neurostimulation is a rapidly expanding field in biomedical engineering, with an estimated market size at present of over $2B (110). Most clinically and commercially successful devices are sensory NPs such as the cochlear stimulator, or they elicit neuromodulatory responses, like TENS and epidural spinal cord stimulators (250). The most widely used *M*NPs are simple muscle stimulators that are used to increase muscle bulk, and provide therapeutic electrical stimulation (TES) with the aim of improving circulation, reducing edema, reducing spasticity and eliciting adaptive changes in neuronal networks in the spinal cord and brain. MNPs that deliver controlled functional electrical stimulation (FES) stimulation to augment or replace voluntary movements are less widely used, partly because of their cost and partly because they may not provide a clear improvement in activities of daily life when compared to alternative therapies and devices such as ankle-foot orthoses. On the other hand, in terms of improving voluntary function in the absence of stimulation, FES is most likely superior to TES, because it is applied in association with voluntary effort. While lower-limb FES competes with mechanical devices such as ankle-foot orthoses and articulated braces, there are no satisfactory mechanical ways of restoring upper limb function, so here there is much potential for development and growth. As the technology of implanted systems improves, it seems likely that spectacular advances will be made in this area in the future.

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