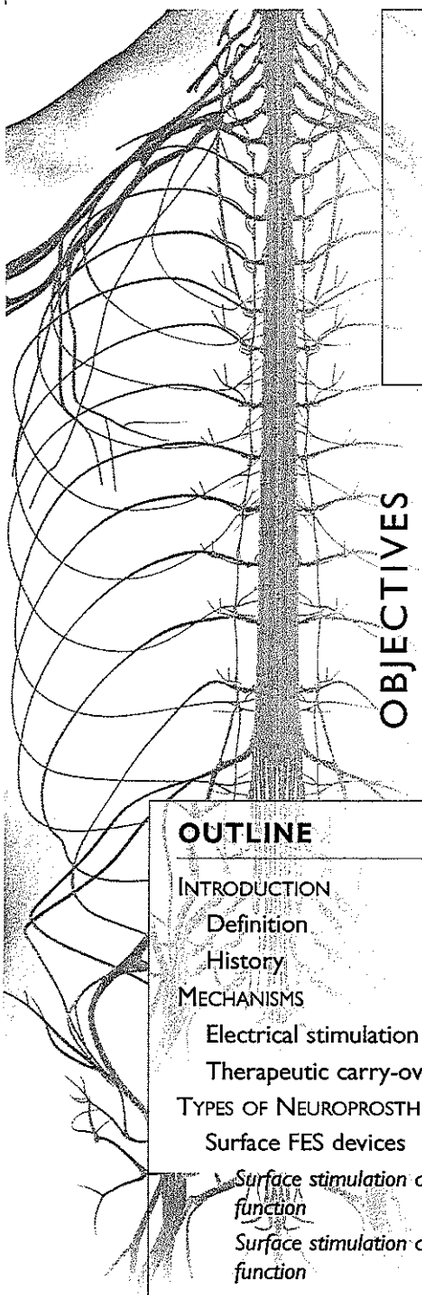

5 Neuroprosthetics

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OBJECTIVES

After reading this chapter, the reader will be able to:

- Understand the basic principles of neuroprostheses (NPs) operation
- Appreciate the historical development of NPs
- Assess the main benefits and limitations of existing NPs
- Recommend the type of NP that might benefit a particular person
- Evaluate new NP technologies as they evolve

OUTLINE

Introduction

Definition

Neuroprostheses (NPs) are electronic devices that stimulate nerves in order to improve bodily functions lost as a result of damage to the peripheral or central nervous system. This approach is also called functional electrical stimulation (FES) or functional neuromuscular stimulation (FNS). NPs include both surface stimulators, which deliver current through the skin to target nerves, and implanted stimulators, which deliver current directly to the target nerves. NPs range from simple "muscle" stimulators used to increase muscle bulk to complex devices implanted in the spinal cord and brain. The aim of this chapter is to describe the numerous types of NPs that have been developed since the early days of therapeutic electrical stimulation (TES), with a particular emphasis on those NPs that are useful in functional restoration after spinal cord injury (SCI). The spectacular advances that have occurred in the neurosciences and in biomedical engineering in the last two decades have led to numerous technical advances and innovations. Surface

and implanted NPs are now available to assist with a wide variety of functions, including hand function, postural control, standing, walking, respiration, micturition, and pain control. This chapter will address issues related to the benefits and limitations of these devices and factors affecting the choice of an NP for a particular individual.

History

Electrostatic machines capable of generating single high-voltage pulses were invented in the 1740s. Clinicians very soon began using them to apply single stimuli through pairs of surface electrodes, more to impress than to provide therapy.[1,2] Michael Faraday's invention of the induction coil in the mid-19th century allowed continuous trains of stimuli to be delivered to nerves and muscles. *Faradic stimulation* quickly became an important means of experimentally stimulating the brain, spinal cord, and peripheral nerves (see "Mechanisms" below).

The first detailed manual of motor points, that is, locations at which faradic stimulation through the skin activated muscles at the lowest thresholds, was published in 1867.[3] Electrical stimulation continued to be used at the fringes of medicine until the 1960s, when the advent of the transistor allowed stimulators to become portable enough to be used in activities of daily life (ADL).

Mechanisms

Electrical Stimulation of Nerves

Faradic stimulation consists of delivering trains of very brief pulses of electrical current through pairs of electrodes applied to bodily tissues. Electrodes applied to the skin surface are made of a conductive material, for example, metal or carbonized rubber, often with a soft conductive material such as a moistened cloth pad or a gel coating that forms an intimate and even contact with the skin surface to prevent hot spots of high-current density. Implanted electrodes are insulated leads with small conductive terminals made of a biologically compatible metal such as stainless steel or platinum-iridium. The terminals are usually built into a nonconductive substrate such as a silastic button (epimysial electrodes), a silastic nerve cuff, or an insulated cannula (brain or epidural spinal cord stimulation).

The voltage produced by a stimulator is the product of current and resistance ($V = IR$). To understand current and voltage, the analogy of water being pushed through a showerhead is useful. In this analogy, the flow of water per second is equivalent to current (I). The pressure drop from inside to outside the showerhead is equivalent to voltage (V). The smaller the holes in the showerhead, the greater the resistance to flow (R) and so the smaller the current. You can force the same amount of water through smaller holes by increasing the pressure inside the showerhead. So flow (current) clearly depends on both the pressure drop (voltage) and resistance. Each pulse of current lasts from 50 to 300 microseconds. Surface stimulation requires currents ranging from 10 to 100 mA and voltages ranging from 10 to 100V, depending on the electrode surface area. Implanted electrodes can activate the nerves they contact with currents in the range 0.1 to 2 mA and voltages in the range 0.1 to 2 V between the electrode terminals. This is because implanted electrodes allow the current to be delivered directly to the nerve rather than being dispersed through a large volume of tissue.

The amount of current required to activate muscle fibers is more than 10 times greater than that required to activate the *nerve* that innervates them, so *muscle* stimulators are really nerve stimulators. Denervated muscles cannot be activated with the pulse amplitudes normally used in FES, so individuals with lesions that have destroyed the relevant motoneuron pools in the gray matter of the spinal cord, or the motoneuronal axons in spinal nerves (as occurs in cauda equina lesions), unfortunately often do not benefit from FES. A single pulse delivered to a motor nerve causes the muscle to twitch once. Repeated pulses cause repeated twitches. Each twitch lasts about 1/20th of a second, so when pulses are repeated at a rate greater than 20 per second, the twitches fuse and the muscle contracts smoothly (this is called a *tetanic contraction* or *tetany*). More force can be produced at higher rates, but the increase levels off at around 35 to 45 pulses/second. Fatigue sets in more rapidly the faster the pulse rate. A good compromise between force and fatigue is usually reached between 30 and 40 pulses/second.

NP stimulators have electronic circuitry that controls either the voltage or current using feedback. If the current is feedback controlled, the voltage is automatically adjusted on a moment-to-moment basis so that the same current is delivered, regardless of the impedance presented by the electrodes and tissue. The result is that if the electrode contact is poor (as an analogy, smaller holes in the showerhead), impedance is high, and so the stimulator automatically increases the voltage to maintain current flow through the smaller contact area. This procedure ensures a constant level of activation of the target nerves but can cause skin burns. On the other hand, if voltage is feedback controlled and electrode contact is poor, the amount of current pushed through is less and the nerve may not be adequately stimulated, but there is little risk of skin burns.

The advantage of current-controlled stimulators is that the device always attempts to deliver the same current regardless of the impedance, thereby ensuring stimulation, but this carries the risk of local tissue damage. Voltage-controlled stimulators always try to deliver the desired voltage. Therefore, if the electrodes make

poor contact, less current will flow. There is no risk of damage to the tissue, but the nerve may not be activated. Often in less-sophisticated stimulators, neither voltage nor current are feedback controlled. On the other hand, in advanced current-controlled stimulators, impedance is monitored and current is limited when the impedance is high.

Therapeutic Carryover Effects

Electrical stimulation of muscles has long been known to have carryover or therapeutic effects,[4–6] especially in conjunction with voluntary exercise training.[7–10] Surface stimulators triggered during attempted functional tasks (Fig. 5-1a) or by voluntary electromyographic (EMG) activity (Fig. 5-1b[11]) have been used in some clinics for FES-assisted motor retraining of the upper extremity.[9,12] The mechanism of carryover is poorly understood. Short-term carryover lasting less than a few hours may result from short-term changes in the energetics of neuromuscular activation, whereas long-term carryover lasting weeks or months is usually attributed to muscle strengthening, neural plasticity, or both.[13–15]

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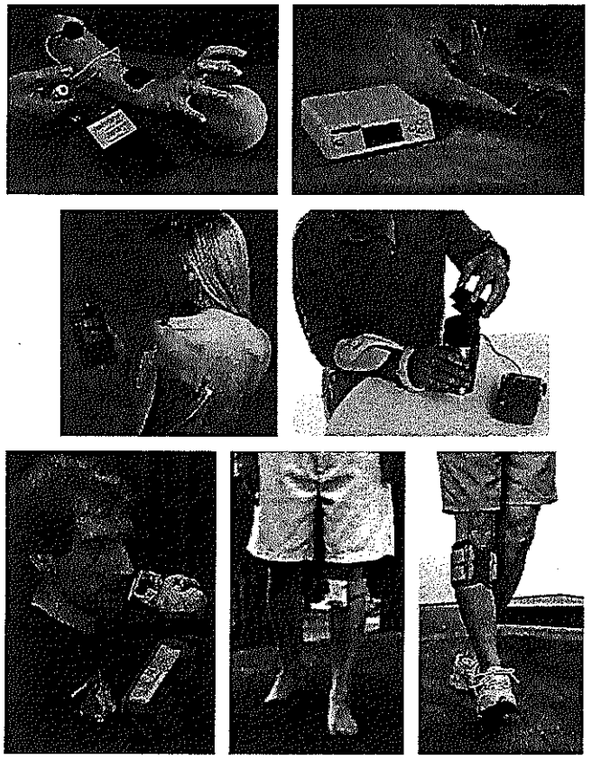

Figure 5-1. Surface NPs. (A) Medtronic, Inc. Respond physiotherapy stimulator; (B) Neuromove EMG-triggered stimulator; (C) Stimulation of trapezius muscle to prevent shoulder subluxation; (D) Ness Handmaster; (E) University of Alberta Bionic Glove; (F) Innovative Neurotronics WalkAide; (G) Bioness L300.

Types of Neuroprostheses

Surface FES Devices

Surface Stimulation Devices for Enhancing Walking Function

The first portable FES device was a surface stimulator that delivered trains of stimuli to the common peroneal nerve to correct foot drop in hemiparetic people.[16] This invention was further developed and commercialized in Europe in the 1960s by a group in Ljubljana, Slovenia (then Yugoslavia) led by Lojze Vodovnik (the FEPO, or functional electrical peroneal orthosis[17]). Since then, portable foot-drop stimulators of various designs have been used by well over 10,000 people worldwide. Most users have been individuals with stroke, though some people with SCI have successfully used them, too. Standard physical therapy stimulators equipped with under-heel sensors to trigger stimulation (and hence muscle activation) appropriately timed to the gait cycle have also been used as foot-drop stimulators in clinics for many years (e.g., the original Medtronic Respond unit and currently the Empi 300PV). By the year 2000, there had been three successful initiatives in countries with public health-care systems to provide foot-drop stimulators to hemiparetic people on a routine basis: Yugoslavia,[18] Denmark,[19] and the United Kingdom.[20] In the United States, a ruling by the Centers of Medicare and Medicaid Services (CMS) in the 1980s precluded reimbursement of neuromuscular stimulators prescribed for neurological disorders (although paradoxically, reimbursement is available when the same devices are used for treating back pain, which generally involves the neuromuscular system). Consequently, adoption of foot-drop stimulators in the United States has been slow and patchy. Currently the three main foot-drop stimulators available in North America on a self-pay basis are the Odstock[21], the WalkAide (Fig. 5-1f[22]), and the Bioness L300 (Fig. 5-1g). They are proving popular and effective, so pressure may increase on CMS to provide a reimbursement code for these aids. They can be effective in individuals with SCI whose main locomotor problem is foot drop.

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The Parastep, a multielectrode bilateral FES stimulator used in conjunction with a walker and controlled by hand switches, was introduced commercially in the 1980s. Up to six muscles were stimulated, three in each leg (foot dorsiflexors, quadriceps, and gluteus medius). The device is primarily used by individuals who have complete paraplegia. These individuals have the arm and hand function required to control the device, and they lack sensation in the legs that would preclude the use of high levels of stimulation. Users must have intact lower motor neuron function in the legs (see Chapter 1). Studies have shown that although ambulation was enabled or improved by this system, the metabolic costs

were generally high.[23–25] A study in France came to the following conclusion: "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, the Parastep can be proposed as a resource to keep physical and psychological fitness in patients with SCI".[26]

Starting in the late 1990s, surface FES has been combined with treadmill training and body weight support for locomotor training. In the first study of its kind on 19 individuals with chronic incomplete SCI (ASIA C), over-ground and treadmill gait speed more than doubled after 3 months of 1.5 hours, 3 days per week, FES plus partial weight-support training.[27] The overall conclusion reached in the SCIRE metastudy[28] on surface FES for gait post-SCI was 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."

Surface Stimulation Devices for Enhancing Hand Function

As with many early FES studies, the first experiments exploring FES for upper extremity function were performed by Vodovnik and colleagues in Ljubljana, Slovenia.[29,30] In the late 1970s, a group at Rancho Los Amigos in Los Angeles, California, developed a therapeutic program for hand function within their clinic, involving dozens of individuals performing daily FES-assisted biofeedback exercises.[31] In the 1990s, two designs of surface stimulator for hand function were developed for people with C6–C7 quadriplegia: the Handmaster (Fig. 5-1d[32,33]) and the Bionic Glove (Fig. 5-1e[34,35]). A clinic-based device, the ETHZ-Paracare, was developed in Switzerland and has undergone two pilot studies.[36,37]

The Handmaster, manufactured by Ness Ltd. in Israel, was medically reimbursed in Holland for several years for use as a functional splint. Recently, this device has been sold to clinics and private users in the United States under the proprietary name Bioness H200. Bioness H200 comprises a hinged wrist-forearm splint with a stimulator box electrically connected to the splint via a cable. Electrodes deployed on detachable panels inside the splint deliver trains of stimuli to combinations of three or four motor points. Stimulation is controlled by a push button on the stimulator or a switch on the part of the orthosis overlying the medial heel of the hand. A recent study in eight individuals with C5–C6 SCI reported significant improvements in hand function after using the Handmaster daily for 3 weeks.[38] Both size and rigid structure make the H200 suitable mainly for use in the clinic as a therapeutic, rather than as an orthotic, device.

The Bionic Glove comprises a fingerless flexible garment with an inbuilt stimulator and electrode contacts. The device is controlled by wrist position (flexion and extension) to augment tenodesis grasp and release. In a pilot study on nine individuals with C6–C7 SCI using the Bionic Glove as part of their usual ADL, grasp force increased fourfold and performance of manual tasks improved significantly during stimulation.[35] In an independent study in 12 individuals with C5–C7 SCI, after 6 months of using the Bionic Glove, voluntary hand function in the absence of the device had improved.[39] Individuals with C6–C7 SCI benefited the most; however, higher functioning individuals were less likely to use the device in ADL because the glove required about 5 minutes to don. Furthermore, even though the Bionic Glove was more formfitting and compliant than the Handmaster, it was still considered too bulky to wear during daily life by some individuals. Various other technical problems were encountered during this 6-month study that led to the overall conclusion that, much like the Handmaster, the Bionic Glove was more useful as a therapeutic/training device than as a permanent orthosis.

A new, more formfitting version of the Bionic Glove is currently being used in a trial involving in-home telesupervised hand exercise therapy in chronic SCI participants in Edmonton, Canada. The device has a smaller inbuilt stimulator approximately the size of an iPod Nano, which is triggered by a wireless transmitter worn behind the ear like a hearing aid. The device detects small voluntary tooth clicks, allowing the user to activate hand opening and grasp independently of wrist position and without involving the other hand.[40] Another improvement is that rather than requiring self-adhesive electrodes to be attached to the skin to make contact with metal mesh panels inside the glove, low-tack gel electrodes are now attached to the inside of the garment. With this new configuration, the system can be donned within approximately 30 seconds. A commercial version will be available to clinical researchers in early 2008. This device has been designed to be used as an orthosis in ADL as well as for therapeutic training.

Multichannel upper extremity FES has been tested experimentally in individuals with C3–C7 SCI.[10] A programmable multichannel stimulator was used to activate muscles in a sequence that allowed reach and grasp. One of the problems with surface stimulation of large muscles such as biceps and triceps brachii is that during activity, the motor points of these muscles can move several centimeters under the skin. This fact changes the relationship between the stimulating electrode and the motor nerve, thereby changing the amount of muscle activation as the elbow flexes and extends. This, in turn, results in problems of control. Nevertheless, encouraging therapeutic results were reported in this study.

Arguably, transcutaneous electrical nerve stimulators (TENS) are NPs too. The mechanism of TENS analgesia is thought to be inhibition of nociceptive transmission in

the spinal dorsal horn by the activation of large sensory axons (the gate theory of pain:[41]). One popular version of electrical stimulation for pain relief is interferential stimulation.[42] The mechanism of interferential stimulation is to set up a rotating electric field that activates large afferents deep within bodily tissues by delivering alternating current through several pairs of electrodes and cyclically varying the currents through each pair independently. This approach is also known as "current steering" or "field steering," when used in implanted dorsal column and cochlear stimulators.[43,44] Interferential devices are usually large, expensive and therefore confined to clinics.

Implanted NPs

General: Cochlear, Phrenic Nerve, Deep Brain, and Sacral Stimulators

In the late 1950s and early 1960s, the first implantable cardiac pacemakers were developed.[45] According to the National Institutes of Health, over 3 million cardiac pacemakers have since been implanted, and the number may be in excess of 5 million. Cardiac pacemakers stimulate specialized cardiac muscle cells; thus, according to the above definition, they are not NPs. However, they are implanted stimulators that must remain functional in the hostile environment of the human body for many years. The development of the technology needed to achieve this quality led to a proliferation of a wide range of NPs in the late 1960s and early 1970s.

Individuals with diverse types of impairment and disability have benefited from the technology associated with the development of the cardiac pacemaker. Thousands of dorsal column stimulators have since been implanted for pain control and spasticity.[46] Dorsal column stimulators activate large sensory afferents in posterior spinal roots and in the dorsal columns. As mentioned above, according to the gate theory of pain, input from large afferents inhibits nociceptive transmission. Modified versions of dorsal column stimulators were later introduced for use as deep-brain stimulators (DBS).[47–49] Several thousand patients have been implanted with DBS devices. DBS is often effective in counteracting tremor and bradykinesia in Parkinson's disease and reducing essential tremor by affecting the firing of neurons in the basal ganglia. Several competing theories have been proposed to explain these effects.[50–52] Phrenic nerve NPs that activate the diaphragm have also been implanted in the thousands (Fig. 5-2b),[53,54] as have vagus nerve stimulators for epilepsy (Fig. 5-2d). Radiofrequency-controlled NPs that stimulated the bladder detrusor muscle were implanted in a small number of individuals in the 1960s.[55,56] In 1997, the Medtronic, Inc. (Minneapolis, Minnesota) InterStim sacral root stimulator (Fig. 5-2c) was approved by the FDA to treat urge incontinence, and since then, according to Medtronic, Inc., 40,000 InterStim devices have been implanted. The InterStim has also been implanted off-label in a small number of SCI individuals in attempts to facilitate voiding (see below).

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The most successful NP remains the cochlear stimulator.[57] In its 2007 Annual Report, Cochlear Corporation (Lane Cove, NSW, Australia) disclosed that by 2006, 100,000 of its stimulators had been implanted. Advanced Bionics had implanted 3,000 of its own cochlear stimulators by 1999. Cochlear stimulators and their associated external sound and speech processors and stimulus synthesizers are now at an advanced stage and provide a model for new generation of NPs for motor control.

Implanted Devices for Enhancing Walking Function

Progress in restoring limb movement with implantable NPs has been slow. The technical challenge of delivering trains of pulses to nerves innervating one or more muscle groups for several hours a day for many years is formidable. A small number of individuals were implanted with foot-drop stimulators in pilot studies in the 1970s and 1980s.[58–60] The Waters and McNeal study[59] commenced in 1968 and led Medtronic, Inc. to develop a sophisticated device called the Neuromuscular Assist, which included an under-heel sensor that wirelessly triggered a portable external receiver/stimulator. This delivered power and stimulus commands through an external antenna taped to the skin to an implanted passive receiver. The receiver delivered pulse trains through a pair of electrodes in a silicone rubber flap wrapped around branches of the common peroneal nerve distal to the knee. Fifteen individuals were implanted. The system worked well in most of the recipients, in some cases for many years, but Medtronic, Inc. decided not to pursue commercialization. Recently, two models of implantable peroneal nerve stimulator have become available commercially in Europe, the Finetech Medical Ltd. (Welwyn Garden City, UK) STIMuSTEP[61] and the Neurodan ActiGait (Figure 5-2a). In a Phase 2 safety study, 15 individuals with foot drop due to stroke were implanted with the ActiGait system and showed improvements in gait.[62] From a safety point of view, the nerve cuffs in the device was reported not capable of producing detectable reductions in nerve conduction velocity. Technical problems occurred, but were resolved at follow-up.[62] Like the Medtronic, Inc. device, the STIMuSTEP and ActiGait stimulators are triggered from an under-heel sensor. A new innovation still at the experimental stage is the use of signals recorded in sensory nerves to trigger stimulation[63,64] (Figure 5-1).

Only a small minority of individuals with incomplete SCI benefit enough from the correction of foot drop alone to warrant the implantation of these devices. Multichannel NPs that stimulate up to 16 muscles of the legs through percutaneous or fully implanted leads have been experimented with over the years,[65–68] but they are not commercially available. However, research in this

area continues, and recent results have been encouraging, particularly in relation to posture, standing, and the avoidance of pressure ulcers (bedsores).[69–73]

Intraspinal Microstimulation

A radically different approach to NPs, namely intraspinal microstimulation (ISMS) has been explored in animal experiments.[74] The method consists of implanting up to 16 microwires in the lumbosacral enlargement of the spinal cord (the region containing motoneurons innervating leg muscles). Stimulation through these microwires can activate single muscles or muscle synergies in normal animals.[75] After some initial promise,[76] several implants in spinalized animals revealed the technical limitations of the approach.[77] The implant surgeries took up to 12 hours. Manually positioning the electrodes in the right parts of the spinal cord to obtain the full set of desired synergies was difficult, and it was rarely completely successful. After days or weeks, the elicited movements changed, indicating migration of the microwires. In a trial in chronically implanted monkeys, co-contraction responses were often seen,[78] which would make it difficult or impossible to control movement in an NP application. The overall impression is that with current electrode technology, ISMS is invasive, insufficiently reliable, and therefore not ready for clinical application (Figure 5-2).

Implanted Devices for Enhancing Hand Function

Regarding the upper extremity, after proof-of-principle trials with percutaneous leads, a fully implanted stimulator was developed at Case Western Reserve University (CWRU) in Cleveland, Ohio.[79] The stimulator was approved by the FDA in 1997 and marketed by NeuroControl as the Freehand System (Fig. 5-2e). About 200 of these systems were implanted in individuals with C4–C5 quadriplegia. Shoulder or wrist movements were used to control the stimulation of muscles in the forearm. An external control unit and antenna wirelessly activated an implanted receiver to generate pulse trains and stimulate the muscles selected by the external controller to produce different types of hand movement. Though all aspects of the technology and surgery were highly advanced, and many recipients benefited significantly with improved hand function,[80] the Freehand System was ultimately withdrawn from the market in 2002. A fascinating analysis of the history of this and other NPs that showed clinical efficacy but did not survive commercially is to be found in a Princeton University thesis by Samuel

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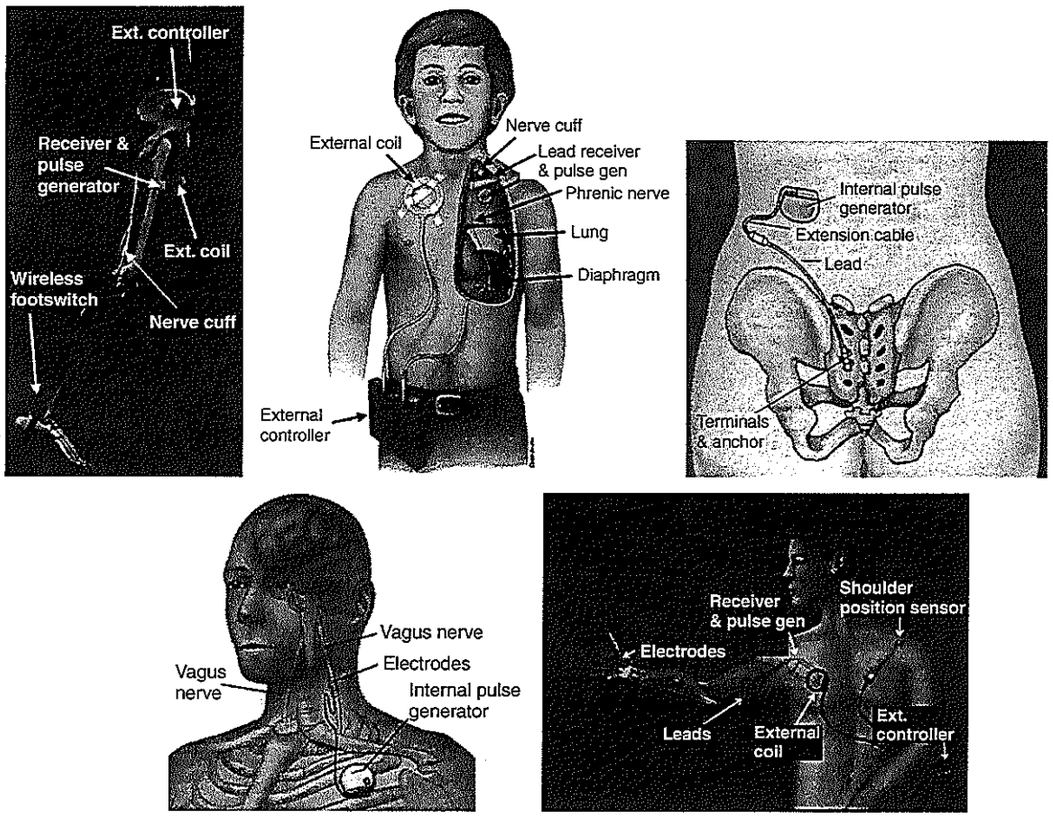

Figure 5-2. Implantable NPs. (A) Neurodan; (B) Avery phrenic nerve pacer; (C) Medtronic, Inc. InterStim sacral nerve stimulator; (D) Cyberonics vagal nerve stimulator; (E) NeuroControl Freehand System.

W. Hall.[81] Hall concludes, "While the over-exuberant health care spending of the 1970s and early 1980s has taught policymakers a valuable lesson, the vicious cost-containment initiatives characteristic of current Medicare policy are outdated and have far-reaching negative effects on public health. The Centers for Medicare and Medicaid Services should replace their anti-technology bias with a payment system capable of recognizing the profound health economic benefits of neuroprostheses."

An improved multichannel version of the CWRU device has recently been implanted in seven individuals with SCI.[82] The new device is controlled myoelectrically (i.e., via signals picked up from voluntarily activated muscles) and activates the biceps muscle as well as muscles controlling hand opening and grasp. Other recent research into novel implantable NPs for hand function include the Finetech Medical Ltd. STIMuGRIP[83] and an implantable system called the Stimulus Router, which requires only the leads to be implanted, using pulse trains coupled through the skin from a wireless-triggered wristlet stimulator[84] (Fig. 5-3). The Stimulus Router system was tested intraoperatively in January 2008 and the first permanent implant took place on June 10, 2008 in a quadriplegic man.[85]

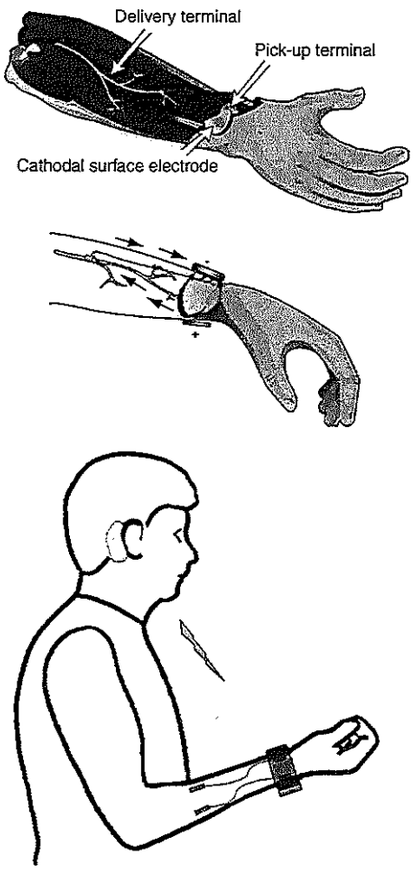

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Figure 5-3. Stimulus router system. (A) Cutaway view showing a surface electrode, implanted pick-up electrode, passive conductor, and nerve cuff. (B) Cross-section showing current flowing between two surface electrodes, some being diverted through the implanted conductor to the nerve cuff and returning via forearm tissues. (C) Schematic showing stimulator cuff containing surface electrodes that deliver current to hand opening and closing nerves via the implanted leads. The cuff is triggered from a wireless earpiece that detects small voluntary tooth clicks.

Bladder Control

Bladder control is ranked the second most significant problem after loss of sex function among individuals with paraplegia and the fourth priority of individuals with quadriplegia.[86] SCI can cause incontinence due to a loss of external urethral sphincter (EUS) contraction and/or an inability to void due to bladder–sphincter hyperactivity (dyssynergia). Untreated, this condition can lead to very high bladder pressures, vesicoureteral reflux, and eventual renal failure. It once was the leading cause of death in people with SCI, but dropped to fourth place after the widespread adoption of clean intermittent catheterization.[87]

Electrical stimulation for bladder control has been explored for over 40 years. Stimulation has been delivered variously to the inside of the bladder, bladder wall, thigh, pelvic floor, dorsal penile nerve, pelvic nerve, tibial nerve, sacral roots, sacral nerves, and spinal cord. The successes and failures of these numerous approaches have recently been described in a detailed review.[88]

The first commercially available NP for bladder control derived from experiments in which voiding was elicited in spinalized animals by stimulation of sacral anterior roots.[89–91] Human trials of a sacral anterior root stimulator implant (SARSI) followed shortly thereafter.[92] Brindley's device was commercialized as the Finetech-Brindley Bladder System (Finetech Medical Ltd). The device has been implanted in over 2500 people, in some cases for over 20 years.[93] The main disadvantage of this device is that dorsal rhizotomies (cutting sensory nerves to the spinal cord) are required, resulting in an irreversible loss of sensory input from the genital organs. Another drawback is that anterior root stimulation activates the EUS as well as the bladder. Voiding is achieved in bursts by taking advantage of the slower relaxation time of the detrusor (bladder) muscle after short trains of stimuli. A recent study has shown that trapezoidal pulse waveforms can activate the bladder more selectively, thus improving the performance of SARSI implants.[94] The permanent nature of procedures that require dorsal rhizotomies have lead many individuals to decline these types of interventions. However, techniques such as pudendal nerve blockade and neuromodulation may soon provide alternative NP types that do not require rhizotomies.

Regarding incontinence, implanted sacral root stimulators (e.g., the Medtronic, Inc. InterStim) are currently the most successful implantable NPs for bladder control in a variety of neural disorders, including SCI.[95]

ISMS has been explored as an alternative means of eliciting voiding, but as in the case of locomotion, ISMS so far has not lived up to initial expectations. Pilot experiments in animals and humans in the 1970s showed that stimulation through pairs of relatively large intraspinal electrodes could elicit bladder contractions, but not without coactivating the EUS.[96,97] More recent experiments have been performed with microwires implanted in the dorsal commissure of the spinal cord, which contains interneurons that inhibit EUS motoneurons.[98] Although reductions in intraurethral pressure could be elicited in some implants, the more common outcome was activation.[88,99] The dorsal commissure was subsequently shown to probably contain more interneurons that excite EUS motoneurons than those that inhibit them.[100,101] In a report published in October 2007, McCreery's group reported success in eliciting bladder contraction, concomitant EUS inhibition, and voiding in two of three spinally transected cats by stimulating mainly within the dorsal columns.[102] However, the voiding trials were performed during deep propofol anesthesia. Urinary tract responses are suppressed by propofol.[103] Bladder and EUS responses to ISMS and pudendal nerve stimulation under deep anesthesia in spinal cord-transected cats can change dramatically when the same animals are awake.[104] Stimuli that relax the EUS under anesthesia are no longer as effective under normal awake conditions. Further evidence in awake SCI animals would be needed before clinical trials could be justified.

Other experimental approaches to bladder control with NPs include neuromodulation of sacral roots;[105,106] activation of reflexes evoked by selective stimulation of specific branches of the pudendal nerve,[107–111] and high-frequency blockade of the pudendal nerve to inhibit the EUS.[112–118] Recently, activation and blockade of the pudendal nerve has been demonstrated with the stimulus router system in the awake SCI cat. This may provide a low-cost type of NP for either maintaining continence or eliciting voiding, as only two leads would be implanted.[117,118]

Factors Influencing Choice

Level of Injury

The level and completeness of SCI will determine the relevance of NPs to a particular individual. Phrenic nerve pacers are only relevant for high cervical injuries, typically at C3 and above. Upper extremity NPs are usually only effective for injuries in the range C4 to C7. Importantly, NPs activate muscles via their nerves. Often motoneurons are destroyed at the epicenter of an injury. This fact is particularly troublesome at segmental level C7, because denervation can make eliciting hand opening and grasping virtually impossible. NPs for restoring locomotion can be useful in incomplete injuries at nearly all levels and also in complete injuries at low thoracic and lumbar levels where postural control is partially preserved. Likewise, bladder control NPs can be useful for nearly all levels of SCI, with the exception of cauda equina injuries, again because these are associated with denervation of the target muscles, in particular the EUS for bladder control.

Time After Injury

There is little evidence-based consensus on the appropriate time after injury at which to commence the use of the various types of commercially available NPs. The same could, of course, be said of conventional physiotherapy. For example, 20 years ago, the accepted wisdom was that gait training should only start at an absolute minimum of 6 weeks after stroke, whereas today it starts as soon as such training is judged clinically to be safe, which can be within a few days in mild cases. Some NPs (e.g., surface muscle stimulators applied to the forearm or shoulder) can be used within a week or two of SCI to maintain muscle bulk and to ward off spasticity, contractures, and shoulder subluxation (see Figure 5-1c). Others (e.g., SARSI implants requiring rhizotomies) should be considered only after natural recovery has been allowed to run its full course (typically 1 year or more after injury).

Risks and Contraindications

Certain side effects or risks of electrical stimulation should always be taken into account when considering the use of NP devices. FES in people with SCI at T6 level and above can trigger autonomic dysreflexia.[119] Originally, this was attributed to nociceptive stimulation of the skin, but topical anesthesia did not change the response to FES, so muscle activation was thought to be the cause.[121] The larger the muscles stimulated, the greater the chance of triggering an episode of dysreflexia. Other side effects include pain or discomfort at high stimulus levels. There is a very wide range of tolerance between individuals in this regard. As to the cost–benefit ratio, although NP design is constantly improving, some devices still tend to be cumbersome and awkward to don and doff. The financial cost can be high, particularly in the case of implantable NPs. Having a clear idea of the functional gains that can reasonably be expected, and weighing these against cost and inconvenience are important.

Supramaximal stimulation of large leg muscles has caused patellar dislocation and even bone breakage in rare cases. Dried-out or faulty electrodes can cause skin burns, particularly in users with poor or lacking skin sensation. Implanted NPs carry a risk of postimplant infection. The risk is well established for cardiac pacemakers (~ 1%[122]) but not so for NPs, which vary considerably in

size and design. Generally, the larger the stimulator and the greater the number of leads, the greater is the risk of infection. Lead breakage and migration tend to occur more in NPs than in cardiac pacemakers, necessitating relocation or explantation and replacement. Implanted microstimulators such as the Bion may also migrate, though how often this might happen cannot as yet be determined.

Despite the growing numbers of implantable NPs and, in some cases, excellent clinical outcomes, some technical and physiological concerns remain. For example, difficulties and risks are involved in implanting multiple electrodes to activate widely distributed peripheral nerves. The long-term effects of chronic stimulation of populations of neurons in the brain, spinal cord, or peripheral nerves remain to be fully explored.

Summary

In this chapter, the historical origins of electrotherapy were briefly reviewed. The basic mechanism of electrical stimulation of nerves was described. Some of the key advances in the development of NPs were identified. The main types of NP used in the management of SCI were considered, and the successes, limitations, and failures of the NP approach were discussed. Finally, some of the factors influencing an SCI individual's choice of NP treatment were reviewed.

It is now recognized that when the use of NPs is combined with other treatments, such as task-related exercise therapy,[27] significant improvements in function can result. In the near future, NPs are likely to be used increasingly in conjunction with surgical procedures such as tendon transfers, pharmacological interventions that reduce spasticity, such as Botox injections and devices that promote exercise training, such as partial weight-support robots and in-home telerehabilitation devices that allow remote supervision and game-playing to improve compliance.[123]

The treatment of incontinence has been one of the success stories of NPs. The control of bladder voiding in people with SCI remains a very important and elusive goal of NP research, but there have been some promising developments in this regard since 2003.

The last decade has seen a big increase in the number of researchers around the world developing new NP devices and approaches. There has also been a significant increase in interest and investment on the part of government agencies and the medical electronics industry in this area. The next decade should see a significant increase in the range and availability of NPs, a lowering of their cost, and an increase in the number and variety of clinical problems they can address.

REVIEW QUESTIONS

1. How effective are NPs in the control of bladder function?
2. Can present-day NPs for the upper extremity provide clinically significant benefits, and if so, does this depend on the cervical level of the SCI?
3. NPs seem very hi-tech. Are therapists and clinicians who have little or no training in electronics, math, or physics likely to understand and use them?
4. What percentage of people with SCI find electrical stimulation uncomfortable or painful?
5. NPs are often very expensive, particularly implantables. What are the payment and reimbursement options?

ACKNOWLEDGMENTS

This work was supported by the NIH, Canadian Institutes of Health Research, Alberta Heritage Foundation for Medical Research, and the International Spinal Research Trust.

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