NEURAL PROSTHESES

Neural prostheses are a developing technology that use electrical activation of the nervous system to restore function to individuals with neurological impairment. Applications have included stimulation in both the sensory and motor systems (Fig. 1) and range in scope from experimental trials in single individuals, as in the case of the visual prosthesis, to commercially available devices placed in thousands of individuals, as in the case of auditory prostheses (Fig. 2). Neural prostheses function by initiation of action potentials in nerve fibers which carry the signal to an endpoint where chemical neurotransmitters are released, either to affect an end organ or another neuron. Thus, neural prostheses are all devices that enable selective and graded control of neurotransmitter release and, in principle, any end organ under neural control is a candidate for neural prosthetic control.

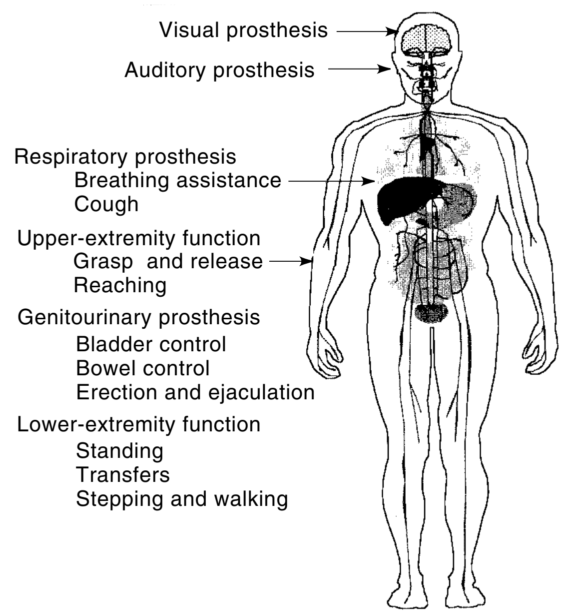

Figure 1. Examples of applications of electrical stimulation of the nervous system to restore function to individuals with neurological impairment.

FUNDAMENTALS OF ELECTRICAL STIMULATION OF THE NERVOUS SYSTEM

The fundamental unit of communication in the nervous system is the action potential, an electrochemical signal that propagates along neurons as a flux of ionic current between the extracellular and intracellular spaces. Artificially generated action potentials can be initiated by electrical stimuli, and will propagate from the site of stimulation in the same way as, and have the same effect as, naturally generated ac-

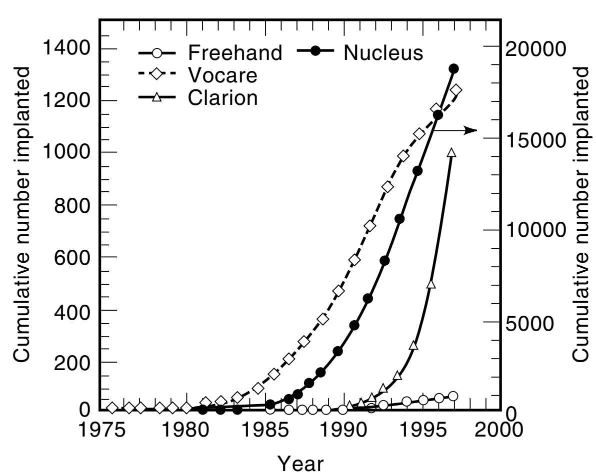

Figure 2. Cumulative numbers of devices implanted for restoration of hand-grasp (FreeHand), bladder and bowel function (Vocare), and restoration of hearing (Clarion, Nucleus). Data for Freehand and Vocare provided by NeuroControl Corp., Cleveland, OH. Data for Clarion provided by Advanced Bionics Corp., Sylmar, CA. Data for Nucleus (right axis) provided by Cochlear Corp., Denver, CO.

tion potentials. Figure 3 shows the responses of a model neuron to two different amplitude stimuli. In response to the smaller stimulus, the neural membrane responds like a parallel RC circuit. However, above a critical amplitude (threshold) the membrane initiates an action potential as a result of flux of sodium ions from the extracellular space to the intracellular space. This action potential is then propagated down the fiber to its terminal where neurotransmitter is released to affect the end organ or another neuron. Artificial generation of action potentials is the basis for all neural prostheses.

The threshold for excitation (i.e., initiation of an action potential) depends on both the amplitude and the duration of the stimulus. As shown in Fig. 4(a), the stimulus amplitude necessary for excitation, I_{th}, increases as the duration of the stimulus, *PW,* is decreased. This relationship is termed the strength–durations relationship and is given by Eq. (1).

$$I_{\mathrm{th}} = \frac{I_{\mathrm{rh}}}{1 - \exp\{-PW/[\ln(2)T_{\mathrm{ch}}]\}} \tag{1}$$

The parameter I_{rh} is the rhoebase current, and is defined as the current amplitude necessary to excite the neuron with a pulse of infinite duration. The parameter T_{ch} is the chronaxie and is defined as the pulse duration necessary to excite the neuron with a pulse amplitude equal to twice the rheobase current.

The amount of charge necessary for excitation can be determined directly from the strength duration relationship and is given by Eq. (2).

$$Q_{\mathrm{th}} = \frac{PW \cdot I_{\mathrm{rh}}}{1 - \exp^{(-PW/T_{\mathrm{ch}})}} \tag{2}$$

The charge required for excitation decreases as the duration of the pulses decreases [Fig. 4(b)]. Thus, short pulses are more efficient at generating excitation. Short pulses also have the benefits of increasing the threshold difference between different diameter nerve fibers, thereby decreasing the gain between stimulus magnitude and the number of nerve fibers activated (1), and increasing the threshold difference between nerve fibers lying at different distances from the electrode, thereby increasing spatial selectivity of stimulation (2). Minimizing charge, by use of short pulses, is an important consideration for preventing tissue damage, preventing electrode corrosion, and minimizing power consumption.

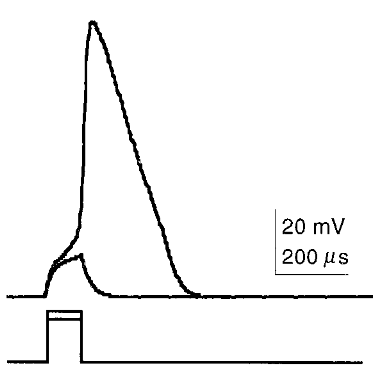

Figure 3. Subthreshold and suprathreshold responses of a nerve fiber to a stimulus current pulse. The traces show the transmembrane voltage as a function of time in response to stimuli of subthreshold and suprathreshold amplitude. In the subthreshold regime, the membrane behaves as a parallel *RC* circuit, while in the suprathreshold regime the membrane generates an action potential.

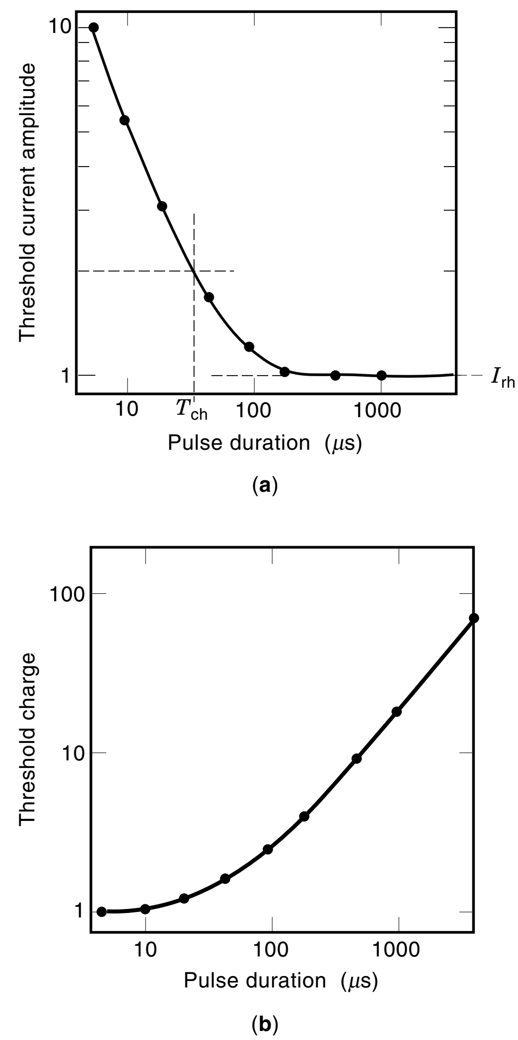

Figure 4. Strength-duration (a) and charge-duration (b) relations for threshold excitation of a nerve fiber.

The current required for extracellular stimulation of axons also depends on the spatial relationship between the electrode and the nerve fiber and the nerve fiber diameter (3). Transmembrane potentials generated by extracellular current are largest in the fibers close to the stimulating electrode, thus less current is required to stimulate neurons in the proximity of the electrode (Fig. 5). As the distance between the electrode and the fiber increases the threshold, I_{th}, increases, and for excitation of myelinated nerve fibers with a point source electrode, this relationship is described by Eq. (3).

$$I_{\mathrm{th}} = I_{\mathrm{o}} + k \cdot r^2 \tag{3}$$

The offset, I_o, determines the absolute threshold and the slope, k, determines the threshold difference between fibers at different distances, r, from the electrode (2).

Similarly, in response to an externally applied stimulus, nerve fibers with a larger spacing between the nodes of Ranvier experience transmembrane potential changes that are

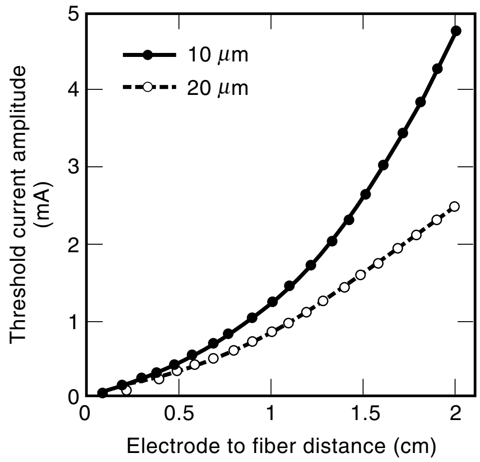

Figure 5. Relationship between the threshold current and the distance between a point source electrode and a nerve fiber in a homogeneous medium ($\rho = 55\ \Omega \cdot \text{cm}$) with the electrode positioned directly over a node of Ranvier.

larger than those in fibers with a smaller internodal spacing. Under normal conditions the larger diameter nerve fibers have larger internodal spacings. Thus when conventional rectangular stimuli are used larger diameters fibers are activated at smaller stimulus amplitudes than the smaller diameter fibers [(Fig. 5(a)].

FUNDAMENTALS OF ELECTRODES AND STIMULUS WAVEFORMS

There are several factors that must be taken into consideration when selecting stimulus waveforms and electrodes for use in a neural prosthesis. The fundamental requirements are that a sufficient change in transmembrane potential be induced to generate action potentials and that the underlying tissue not be damaged by the electrode or stimulus.

Neural prosthesis electrodes require a conductor for current delivery, an insulating carrier for the stimulating element, a conductive lead, and lead insulation. Electrodes must provide selective, graded, and maximal activation of the targeted tissue in a stable and repeatable manner with minimal activation of neighboring tissue. Implantable electrodes must be both passively and actively biocompatible. Passive biocompatibility refers to the tissue reaction to the composition, shape, and mechanical properties of the electrodes materials, while active biocompatibility refers to the performance of the device under stimulation. A polarization voltage develops across the electrode–tissue interface when current is passed through the electrode. Therefore, a regulated current waveform should be used with implanted electrodes to ensure that the electric field generated in the tissue is independent of electrode polarization. However, regulated voltage waveforms should be used when surface electrodes are used to minimize the possibility of skin burns if an electrode becomes dislodged.

Passage of current through the electrode may cause electrochemical reactions that lead to the formation of toxic chemical species around the electrode, corrosion of the electrode material, or activation of tissue to a level that causes neuronal damage (4). Metal electrodes carry current via electrons, while in the body current is carried by ions. Therefore, at the electrode–tissue interface, charge transfer from electrodes to ions must occur. Certain interfacial reactions may be reversed by using a charge balanced, biphasic stimulus pulses, and thus stimulation may occur without tissue damage. However, irreversible reactions may occur even with the use of biphasic stimuli and waveforms must be designed within established safety limits (5,6)

MOTOR SYSTEM NEURAL PROSTHESES

Restoration of Limb Movement Function

A number of diseases and injuries can impair the ability of the nervous system to control movements of the limbs, preventing affected individuals from performing many routine tasks requiring movements of the limbs, such as standing, walking, and manipulation of objects by the hands and arms. Conventional rehabilitation methods provide good solutions to some problems (e.g., wheelchairs for routine ambulation), but individuals with movement disabilities must rely on assistance from others for many routine tasks. Neural prostheses based on functional neuromuscular stimulation can restore some of these movements, offering users increased independence in daily activities and the potential economic benefits of lower attendant costs and improved occupational opportunities.

Neural Control of Movement and Disorders. The nervous system normally controls movement using a number of parallel mechanisms, including voluntary commands produced at a conscious level, locomotion commands produced at a semiconscious level, and reflex responses (e.g., the knee jerk) at an unconscious level. However, all neural control systems ultimately activate the same muscles in order to produce their effect, and therefore all converge upon the "final common pathway" represented by the several hundred motoneurons which typically innervate a muscle. Disorders which result in impaired movement function can occur at a number of sites in the chain from the brain down to the muscle fibers. All current movement neural prostheses substitute artificial electrical activation of the peripheral end of this chain (usually of the motoneurons themselves) for the normal activation by the nervous system, and are thus applicable only to lesions that spare the muscles and motoneurons. Thus, neural prostheses are not currently used to restore functions lost by diseases or injuries of the muscles (e.g., muscular dystrophy) or the motoneurons themselves (e.g., brachial plexus injury). Although neural prostheses could potentially improve movement function in a number of neurological disorders (e.g., cerebral palsy), the two primary applications to date are stroke, with approximately 60,000 new cases per year with moderate to severe permanent impairment, and spinal cord injury (SCI), which affects 7,500 to 10,000 individuals per year. Both of these conditions tend to be stable after the initial insult, although the impairments due to stroke and SCI are somewhat different. Stroke normally affects one side of the body only (producing hemiplegia) and is often accompanied by cognitive, speech, and other disorders. Sensory function is usually spared in individuals with stroke, and muscles in different parts of the limb can be paralyzed, weak, or simply difficult to activate in a coordinated manner. SCI tends to occur in younger individuals and the level of movement impairment depends upon the location of the injury. SCI at thoracic (mid-back) or lower levels results in paraplegia (paralysis of the legs and pelvis), while SCI at cervical levels results in tetraplegia (also known as quadriplegia—paralysis of the legs, trunk, and arms). Within either paraplegia or tetraplegia, the level of impairment increases as the level of spinal cord injury progresses toward the head. SCI can be complete (i.e., interrupting all communication with the brain) or incomplete (i.e., some communication with the brain is retained). Both motor and sensory functions are typically affected.

Design Challenges for Movement Neural Prostheses. The design of neural prostheses must take into account a number of physiological changes that accompany neurological disorders, as well as limitations in the current technology for artificially exciting the nervous system. Following stroke or SCI, paralyzed muscles undergo *disuse atrophy,* characterized by a rapid and marked decrease in muscle mass, a decrease in force-generating capacity, and increased susceptibility to fatigue (7,8). In SCI, denervation occurs when direct physical damage due to the injury or its subsequent consequences (swelling, release of various chemical factors, etc.) leads to the death of motoneurons in and near the area of injury (8). As the motoneurons degenerate, the muscle fibers they innervate can no longer be activated by the nervous system, and electrical activation is difficult or impossible. The disuse of limbs because of paralysis often leads to a rapid reduction in bone density (osteoporosis), which is especially of concern in lower extremity neural prostheses because of weight bearing and the large muscle forces required. Disuse of a limb also often results in an increase in the passive resistance of joints to movement (contractures), which may make it difficult for already weakened muscles to move the limb through its needed range. Paralyzed or paretic muscles are often spastic, that is, have hyperactive stretch reflexes causing inappropriate muscle contractions or spasms. All currently available neural prostheses recruit the motor units within the muscle in an order reverse that of natural recruitment. In many muscles, full activation via electrical stimulation cannot be achieved without undesirable spillover to other muscles, limiting the forces available. Usually, the number of stimulation channels available is far less than the number of muscles normally participating in the movement function, so simpler alternate strategies for completing functional tasks must be developed. Many tasks also involve the simultaneous movement of several different joints, all of which may be impaired. Providing the user with reasonably natural control over all these functions simultaneously can be a significant challenge.

At least partial solutions to each of these problems have been developed. Exercise of paralyzed muscle by electrically stimulated contractions for 2 to 8 hours per day has been found (7,9) to make the muscle more resistant to fatigue, although increases in force appear to occur consistently in some muscles but not in others. The effects of denervation following SCI may be partially compensated by sprouting, a process by which surviving motoneurons in a muscle reinnervate nearby denervated muscle fibers and thus maintain their ability to produce force when electrically stimulated. In the upper extremity, muscle tendon transfer of a nondenervated (either voluntary or paralyzed) muscle can sometimes be performed to replace the function of a denervated muscle. Appropriate weight bearing and exercise can arrest and perhaps even reverse bone demineralization. Joint and muscle contractures can often be prevented by appropriate therapy, including movement through the range of movement. Surgical procedures can also be performed in some cases to release tight joints (10). Spasticity can often be controlled pharmacologically.

Movement Neural Prostheses, Past and Current. Neural prostheses have been developed for restoring specific movements of both the upper and lower extremities, as summarized in Table 1. Applications for upper extremity movements have historically focused on hand grasp and release, primarily in individuals with cervical SCI. Several systems are currently available for providing these functions, including two that are based upon surface electrodes, one using percutaneous electrodes and an external stimulator, and one using a totally implanted stimulator and implanted electrodes. The surface systems are relatively inexpensive and are noninvasive since no surgery is required. However, they require accurate electrode placement before each use, and individuals with denervation may not be able to use the system. The Handmaster (Ness Ltd.) (11,12) device has been used in individuals with C4 to C7 SCI, and in hemiplegia. The Tetron Glove (Neuromotion, Inc.) (13) utilizes voluntary wrist function of the user to control the stimulation, so its applications are primarily limited to C6 to C7 individuals and those with hemiplegia. The percutaneous electrodes used by Handa, Hoshimiya, and associates at Tohoku University (12,14) offer higher selectivity and can reach deeper muscles inaccessible from the surface, and are relatively inexpensive because the electrodes are implemented without open surgery. Muscle-stimulation patterns are based on templates of natural muscle activation, so separate templates must developed and stored for each task to be performed. This system has been applied to individuals with cervical SCI (C4 to C6) and hemiplegia to produce hand, forearm, elbow, and shoulder function. The Freehand (NeuroControl, Inc.), developed originally by Peckham and associates (7,15) uses 7 to 8 implanted epimysial stimulating electrodes and a pacemaker-like stimulator implanted in the upper chest to restore two grasp patterns (key grip and palmar grasp) for individuals with C5 to C6 level SCI. Power and stimulus commands are transmitted electromagnetically via a skin-mounted antenna to the implanted stimulator. Stimulus patterns are controlled voluntarily by the user via a joystick-like device mounted on the opposite shoulder or on the ipsilateral wrist. This implanted technology is more expensive and invasive than the other alternatives, but it is highly reliable, has few external components, and is thus easy to put on and take off. Furthermore, the implant procedure is usually performed simultaneously with reconstructive surgeries such as muscle tendon transfers (10) to maximize voluntary and stimulated contractions, and to release passive constraints. Continuing research with this system is extending its functionality to include stimulation of intrinsic hand muscles, wrist function, forearm function, elbow function, shoulder function, and bilateral hand function. The use of implanted sensors is being investigated, and the use of movement neural prostheses is also being extended to individuals with hemiplegia and different levels (C3 to C4, C7) of SCI.

A number of neural prostheses for lower extremity function have also been developed. As noted in Table 1, several

Table 1. Summary of Past and Current Movement Neural Prostheses

Group or Company	References	Electrode Type	Stimulator Type	User-Control Method	Functions	Disorders	# Systems
Ness, Ltd. Handmaster	11	Surface	External	Preprogrammed	Hand-grasp and release	HP, SCI	120
Neuromotion, Inc. Tetron Glove	13	Surface	External	Write motion	Hand-grasp and release	HP, SCI	47
Tohoku Univ. research	14	Percutaneous	External	Preprogrammed	Hand grasp and release, arm movements	HP, SCI	~25
NeuroControl, Inc. Freehand	7,15	Implanted	Implanted	Contralateral shoulder motion	Hand grasp and release, elbow extension, surgical reconstruction	SCI	~85
Cleveland VA/CWRU research	7,39	Implanted, percutaneous	Implanted and external	Implanted sensors, voluntary function	Improved hand grasp, bilateral function, proximal arm functions	SCI, HP	~65
Univ. Aalborg research	37,38	Percutaneous	External	Nerve recording	Hand grasp with slip compensation	SCI	2
Various research surface systems	early work	Surface	External	Foot switch	Foot drop	HP	>250
Elmetec A/S Footlifter	commercial	Surface	External	Foot switch	Foot drop	HP, MS	3800
NeuroMotion, Inc. Walkaide	commercial	Surface	External	Tilt sensor	Foot drop	HP, MS	40
Medtronic/Rancho implant	19	Implanted	Implanted	Foot switch	Foot drop	HP	31
Ljubljana implant	17,18	Epineural	Implanted	Foot switch	Foot drop	HP	>50
Univ. Aalborg Research	38	Surface	External	Nerve recording	Foot drop	HP, MS	2
Ljubljana hemiplegia systems	16	Surface	External	Foot switches, hand switches	Standing, walking, foot drop	HP	2500
Ljubljana SCI systems	20,21	Surface	External	Foot switches, hand switches	Standing, walking, foot drop	SCI	~250
Sigmedics, Inc. ParaStep	22	Surface	External	Hand switches	Standing, walking	SCI	300
Cleveland VA/CWRU research	23,24,26,27	Implanted	External and implanted	Hand switches	Standing, walking, stair climbing	SCI, HP	50
Shriners Hospital (Philadelphia)	Betz and associates	Implanted	External, implanted	Hand switches	Standing, walking	SCI, HP	20
Davis et al.	28	Implanted epineural	Implanted	Laboratory	Standing	SCI	2
LARSI	29	Implanted spinal root	Implanted	Laboratory	Basic research	SCI	~10
Vienna group	30	Epineural	Implanted	Hand switches	Standing, walking	SCI	4
LSU-RGO II hybrid	31	Surface	External	Hand switches	Standing, walking	SCI	70
Andrews et al. hybrid	32	Surface	External	Automatic sensor-based	Standing, walking	SCI	2
Cleveland VA/CWRU research hybrid	23,24	Percutaneous, implanted	External, implanted	Hand switches	Standing, walking	SCI	6

The numbers of systems listed are cumulative and not limited to current users. Some studies have been discontinued. Some subjects have used more than one system and thus may be counted more than once. References may not contain most recent number of systems, which were in many cases obtained via personal communication.
HP = hemiplegia; SCI = spinal cord injury; MS = multiple sclerosis.
LARSI = Lumbosacral anterior root stimulator implant; LSU-RGO = Louisiana State University Reciprocating Gait Orthosis; CWRU = Case Western Reserve University; VA = Dept. of Veterans Affairs.

groups have developed systems for overcoming "foot drop," a condition which often accompanies stroke or incomplete SCI due to the inability of the ankle to dorsiflex and raise the toes and feet off of the ground during the swing phase of gait. In all of these systems, an external sensor (usually a contact switch in the shoe) detects when the foot is off the ground, triggering stimulation of the common peroneal nerve through surface (16) or implanted (17–19) electrodes. The peroneal stimulation activates the muscles which produce ankle dorsiflexion, and also evokes a flexion withdrawal reflex (due to excitation of sensory fibers within the nerve) which causes the ankle, knee, and hip all to flex and further raise the foot off the ground. At least two commercial systems are currently available. The Footlifter (Elmetec A/S) is a two-channel surface system using a foot switch. The Walkaide system (Neuromotion, Inc.) uses a tilt sensor built directly into the stimulation unit. More than 5000 individuals have used foot-drop neural prostheses.

Stimulation of the peroneal nerve has also been used as part of a system for restoring standing and walking in individuals with hemiplegia or thoracic SCI (20–22). The user stands up using stimulation of the quadriceps muscles to lock the knees, in combination with upper-body exertion. During walking, the flexion withdrawal reflex is evoked alternately in each leg by two channels of stimulation to allow the non-weight-bearing foot to clear the ground, substituting for the swing phase of gait. Quadriceps stimulation is used to lock the knee during the weight support phase of gait. All forward progression is provided by voluntary actions of the upper extremities, not by lower-extremity contractions, and a rolling walker or crutches are required for support and stability. Hand or foot switches are used by the subject to elicit the stimulus pattern for each leg to produce the stepping movements. A commercial system based on these principles, the Parastep device (Sigmedics, Inc.), is currently available (22).

Neural prostheses based upon surface stimulation cannot access anatomically deep muscles, challenge the tolerance of the user for applying the electrodes daily, and require repeatable electrode placement from day to day. The flexion reflex also tends to decline in strength (accommodate) during the repeated activation required during gait. Several groups, most notably the Cleveland VA–Case Western Reserve University group (23–27) and the satellite Shriners group have developed lower-extremity neural prostheses based upon permanent percutaneous and/or implanted electrodes to address these concerns. Forward progression is aided by active contractions in lower-extremity muscles, although all users employ a walker or crutches for stability and safety. Lower-extremity FNS systems employing percutaneous intramuscular electrodes have been shown to restore standing, walking, and stair climbing, as well as side- and back-stepping motions to individuals with paraplegia. The percutaneous electrodes used in these systems can be introduced in a minimally invasive manner via hypodermic needles (23). The use of implanted stimulators and electrodes surgically implanted within or on the muscle, or on spinal roots or peripheral nerves has been investigated by several groups (25–30).

Restoration of gait using electrical stimulation is metabolically inefficient, and the number of motions that must be controlled during any lower-extremity action is typically more than can be produced by the available number of stimulation channels. All current lower-extremity neural prostheses use external support of some kind, usually a rolling walker, but several groups (31–33) have combined the actions of FNS with more extensive external braces such as reciprocating gait orthoses (RGOs) to produce *hybrid* systems. The external braces provide stability, while stimulated contractions of lower-extremity muscles provide the power for walking and standing up without assistance. Although RGOs (and other braces) used with or without electrical stimulation are relatively inexpensive and are often successful in allowing users to stand and walk with fairly low energy consumption, their long-term usage rate has been low because they are difficult to put on and take off, they are often cosmetically unacceptable to the users, and they work well only over flat, even surfaces.

Future Directions. Future clinically available movement neural prostheses will incorporate the most useful features that emerge from current research projects. "Useful" features will be those that extend the benefits of neural prostheses to individuals with different disabilities (e.g., higher level SCI, incomplete SCI, stroke, cerebral palsy), provide additional functions not currently available (weight shifting, transfers, more dexterous hand function, proximal arm function, unassisted standing), enhance reliability, incorporate simpler and more natural user interfaces, and reduce costs. Reliability of movement neural prostheses will be enhanced by implantation of most of the system components (e.g., electrodes, stimulator, sensors for control). Lost-cost surface systems will be effective in some individuals, but the effectiveness of neural prostheses will continue to be greatly enhanced by reconstructive surgeries. Limitations in current stimulation technology, such as spillover and incomplete activation, may be addressed by specialized nerve cuff electrodes (34) or other approaches that selectively target motoneurons within the nerve trunks rather than in the muscle. Routing leads to an ever-increasing number of electrodes may be addressed by leadless injectable electrodes (35) or other approaches which do not require a separate lead wire from the stimulator to each electrode. Control methods will integrate with and make full use of retained voluntary control. Signals recorded from natural sensory receptors in the paralyzed limbs (36–38) and/or from external or implanted artificial sensors will be used both as command signals from the user and to implement closed-loop or feedforward controllers (33,39–43) to compensate for internal (e.g., fatigue) and external (e.g., unexpected loads) disturbances.

Bladder and Bowel Function

Loss of control of bladder and bowel function occurs after spinal injury, and is one of the leading causes of morbidity and mortality. Complications include frequent urinary tract infections, incontinence, damage to the upper urinary tract, and constipation. A number of approaches using electrical stimulation to restore bladder function in individuals with spinal cord injury have been attempted and are outlined in Fig. 6 (44,45). Many attempts have been hampered by direct or reflex activation of the urethral sphincter, which closes the outlet from the bladder, at the same time as the bladder is con-

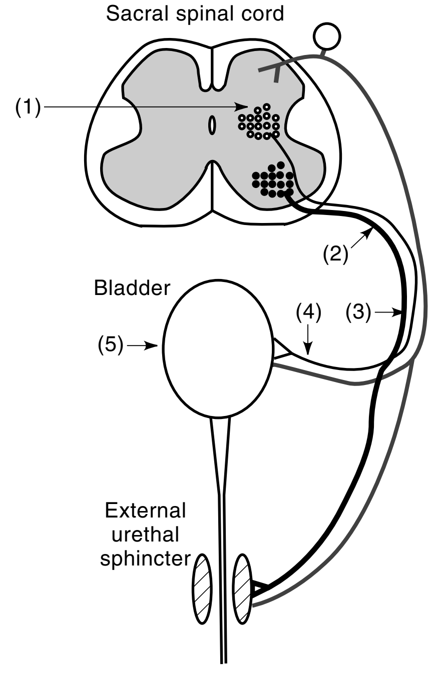

Figure 6. Approaches to neural prosthetic control of the bladder include stimulation of the spinal cord (1), stimulation of the intradural (2), and extradural (3) sacral nerve roots, stimulation of the pelvic nerve (4), and direct stimulation of the bladder wall (5).

tracting trying to force urine out, thus preventing the bladder from emptying. However, significant clinical benefit to large numbers of individuals has been achieved by electrical stimulation of the sacral nerves innervating the lower urinary tract (46).

The first approach to bladder emptying is direct stimulation of the bladder wall. This technique met with limited success and has virtually been abandoned, although it may be useful in cases of denervation of the bladder. The failure of this approach was primarily due to the small region of the bladder activated by direct stimulation and the difficulty of creating stable and reliable electrical interfaces in contact with the bladder wall. The second approach is direct stimulation of the pelvic nerves. While this would seem to be the most logical method to generate selective activation of the bladder, this approach has been hindered by difficult surgical access to the nerve, difficulty in interfacing with the small, branching pelvic nerve, and unwanted cocontraction of the urethra, presumably due to activation of pelvic afferent fibers. The third approach that has been attempted is direct stimulation of the spinal cord using penetrating electrodes. Pairs of electrodes were implanted into the gray matter of the sacral spinal cord to stimulate the preganglionic parasympathetic innervation of the bladder. Good results were achieved in 16 of 27 patients followed for as long as 10 years, but no further implants have been performed (47). Intraspinal microstimulation for control of bladder function is an active area of research and development (48,49).

The location where electrical stimulation has produced the most success is the sacral spinal nerve roots, either intradurally on the ventral (motor) roots or extradurally on the combined root. The sacral roots contain the small-diameter preganglionic parasympathetic axons innervating the bladder via the pelvic nerve and the larger diameter somatic motor axons innervating the external urethral sphincter via the pudendal nerve (Fig. 6). Since large fibers have a lower threshold for excitation (Fig. 5), sacral root stimulation at low amplitudes results in activation of the urethral sphincter, while higher-stimulus amplitudes lead to contraction of both the bladder and the urethral sphincter, leading to little or no voiding.

Several methods have been tested to overcome the coactivation of bladder and external sphincter caused by sacral root stimulation including surgical transection of the pudendal nerve, electrical block of pudendal nerve transmission, stimulation induced fatigue of the sphincter, and intermittent stimulation. Each approach has shortcomings, but intermittent stimulation has achieved widespread success in emptying the bladder via poststimulus voiding (44). This technique takes advantage of the difference in the speed of contraction and relaxation of the bladder and external urethral sphincter. The bladder consists of smooth muscle and thus contracts and relaxes slowly, while the external urethral sphincter consists of striated muscle and contracts and relaxes quickly. Intermittent stimulation (3 s to 6 s on, 9 s off) leads to sustained contraction of the bladder but relaxation of the sphincter between stimuli. Thus urine passes in the interburst interval and the bladder is emptied in spurts.

The technique of intermittent stimulation has been combined with transection of the sacral dorsal (sensory) roots to provide effective bladder control in large numbers of individuals (46). In addition to the ability to urinate when desired, this treatment also produces reductions in posturination residual volumes, urinary tract infections, bladder trabeculation, and vesicoureteral reflux, and increases bladder capacity and continence (44). Furthermore, since the lower bowel also receives efferent innervation from the sacral roots, many patients using the stimulator have an increased frequency of defecation, a reduction in constipation and fecal impaction, and a reduction in time spent defecating (44). Penile erection is also achieved by stimulation in some male users.

The other technique under active investigation to prevent coactivation of the bladder and external urethral sphincter is selective stimulation of the small fibers innervating the bladder (50). Selective stimulation of small fibers may be achieved by arresting action potentials in large fibers (51) or by elevating the threshold of large fibers above that of the small fibers (52). These techniques should enable selective contraction of the bladder or lower bowel without contraction of the external sphincters, and thereby produce better emptying.

Restoration of Respiratory Function

Maintenance of respiratory function is essential for life. Breathing provides the lungs with fresh air for the exchange of oxygen with carbon dioxide in the blood so that all cells of the body can function. Coughing is used to expel foreign substances and normal secretions from the lungs and thus prevents obstructions and infection. If respiratory muscle function is inadequate, a mechanical respirator is often used to force air into and out of the lungs. Although mechanical ventilation can maintain life, the individual is continuously dependent on the respirator, and its use can lead to infection and bleeding around the tracheotomy site, trauma to the bronchi within the lungs, and impaired speech and sense of smell. Impaired cough can lead to obstruction of portions of the lung and/or pneumonia.

If respiratory impairment results from inadequate activation of the motoneurons of the respiratory muscles, neural prostheses based upon electrical stimulation are often a viable option for long-term respiratory maintenance. Such systems allow users to decrease or even discontinue the use of mechanical ventilation, reducing its side effects and significantly enhancing their independence. More than 1000 individuals worldwide have been provided with neural prostheses that control paralyzed diaphragm function via stimulation of the phrenic nerve (53–56). The primary applications for these devices have been individuals with high-level cervical (C3 or above) spinal cord injury, in whom the diaphragm is paralyzed while the phrenic motoneurons remain intact, and in individuals with central alveolar hypoventilation, where the brain fails to activate the muscles of respiration due to a deficit in the chemoreceptors in the carotid body.

All commercially available phrenic pacing systems work using the principals illustrated in Fig. 7. Electrodes are implanted upon the phrenic nerves, with lead wires from the electrodes running under the skin to an implanted pacemaker-like device that generates the electrical stimuli. The stimulators receive power and commands from an external controller via an electromagnetic link. In all of these systems, stimulus parameters are set by the clinician to achieve adequate and smooth recruitment of the diaphragm. Stimulation of the diaphragm (see Fig. 7) acts to expand the volume of the chest cavity, lowering chest cavity pressure below atmospheric pressure and resulting in air flow into the lungs. The

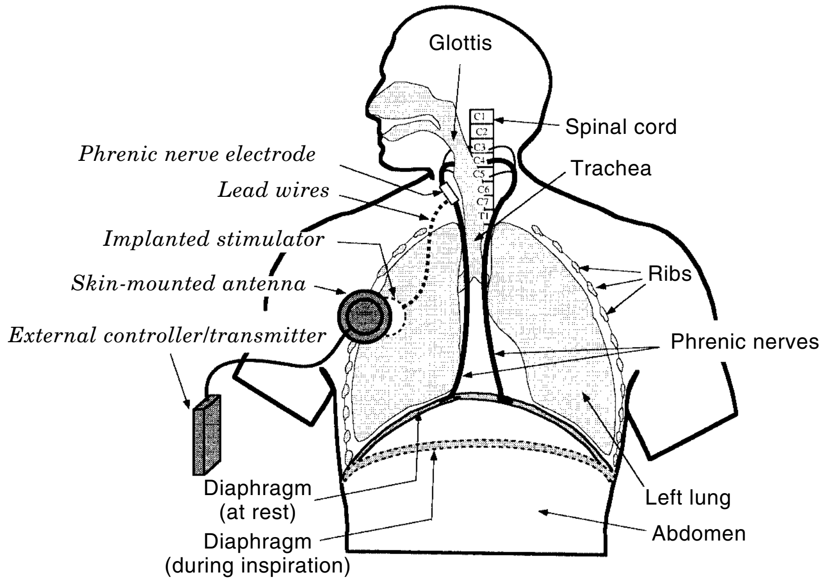

Figure 7. A schematic diagram of the respiratory system and a typical phrenic nerve pacing system. Inhalation is provided to individuals with paralyzed diaphragms by stimulation of the phrenic nerve (usually on both sides) via an electrode implanted onto the nerve. An implanted stimulator receives power and stimulus commands from a small external unit via an electromagnetic link across the skin. Stimulated contractions of the diaphragm pull it down into the abdomen, drawing air in through the mouth and nose. Exhalation occurs passively when the diaphragm stimulation is withdrawn and the elastic properties of the lungs and chest wall force air out of the lungs.

elasticity of the stretched lung tissue and surrounding chest wall passively force the air back out during expiration when the diaphragm is relaxed. System users are typically given control over the number of breaths per minute and duration of each breath to adjust for different levels of exertion. The different phrenic nerve pacing systems vary mainly in the type of electrode used and in the stimulation methods used to rotate or alternate stimulation among portions of the diaphragm to reduce the danger of fatigue (55).

Current research is aimed at improving the function of currently available neural prostheses, making them safer and cheaper to install, and expanding the range of individuals who might benefit. Work is in progress to make phrenic pacing systems fully implantable to reduce the danger of accidental uncoupling from the external control unit (55). Intramuscular electrodes inserted into the diaphragm (57) have been proposed as alternatives to phrenic nerve pacing that have a lower potential for damaging the phrenic nerve and may be less invasive to implant. Intercostal (58) and/or abdominal (59) muscle stimulation has been investigated as a method of providing respiration in individuals with very weak or completely denervated diaphragm muscles, and as a method for improving cough (60,61). Future work will likely focus on making respiratory neural prostheses automatically responsive to metabolic demands and on using remaining nonparalyzed respiratory function to trigger stimulation in a natural and volitional manner.

SENSORY NEURAL PROSTHESES

Auditory Prostheses

The neural prosthesis having the most widespread use and largest numbers of users is the auditory prosthesis. The vast majority of auditory prostheses are cochlear implants which electrically activate the auditory nerve via electrodes implanted within the peripheral organ of the auditory system, the cochlea. Cochlear implants are intended for individuals who are sensorineurally deaf—that is, the hair cells of the cochlea, which transduce sound in the form of vibrations into neural action potentials, are impaired, while the nerve fibers innervating the hair cells are largely preserved. The surviving auditory neurons, or spiral ganglion cells, can be stimulated to fire action potentials by application of stimuli of the appropriate magnitude, duration, and orientation, and these artificial action potentials evoke the perception of sound. For individuals without an intact cochlear nerve, a central device, with electrodes placed in the cochlear nucleus has also been developed.

Modern cochlear implants consist of three primary components: (1) an external processor and transmitter, (2) an implanted receiver stimulator, and (3) an implanted electrode array. The external processor and transmitter collects sound signals with a microphone, processes them with an algorithm to convert the most salient features of the sounds into a pattern of electrical stimuli, and transmits the appropriate command information to the implant. The implanted stimulator receives the information, decodes it, and applies the appropriate stimulus current to the implanted electrode array.

Early cochlear implants used a single-channel electrode and provided functional benefits to most users (62). Perceptual experiments, in which speech was simulated by means of a small number of amplitude modulated single-tone generators, suggested that at least six channels were required for speech comprehension (63). Therefore, modern cochlear implants use multiple-channel electrodes designed to take advantage of the tonotopic organization of the cochlea (64). The cochlea is organized such that the basal region responds to high-frequency sounds, while the apical region responds to low-frequency sounds. This tonotopic arrangement converts place information to frequency (or pitch) information and is referred to as the place-pitch theory. Therefore, with a multiple electrode array, the perceived pitch is related to where within the cochlea the stimulus was applied.

Multichannel cochlear implants, combined with modern speech processors, have been remarkably successful, and are currently implanted in over 20,000 individuals worldwide. In the most successful cases these devices enable open speech recognition without the aid of lip reading, and even use of the telephone (65). However, the performance with the same devices implanted in different individuals varies widely across individuals, and performance is also very dependent on the user's environment (66). The reasons for these differences are not clear and are an area of active research. Future advances in cochlear implants will likely include new speech-processing strategies, new arrays that place electrodes as close as possible to the excitable fibers, and new stimulation techniques that enable selective stimulation of discrete groups of cochlear nerve fibers. Although the cochlea is organized tonotopically, the ability to stimulate selectively discrete groups of nerve fibers and thereby evoke different frequency percepts, is difficult due to current spread within the cochlea. Bilateral implants are also likely to produce increases in function, as in hearing individuals the second ear makes it possible to distinguish multiple sound sources by their relative locations.

For individuals without an intact cochlear nerve—for example due to removal of a tumor—a central device has also been developed. This auditory prosthesis uses electrodes placed on the surface of the cochlear nucleus, the first-order projection site of auditory nerve fibers. These devices have been used in far fewer individuals than cochlear implants, but apparently provide similar performance and benefits (67,68).

Visual Prostheses

Electrical activation of neurons within the visual system is currently the only technique to restore vision to profoundly blind individuals. Experimental work on developing a visual prosthesis was pioneered by Brindley and Lewin (69), who implanted an array of 80 electrodes on the surface of the visual cortex in a blind volunteer. These experiments demonstrated that electrical stimulation of the cortical surface produced phosphenes (bright spots of light) in the visual field of a blind volunteer, and that there was a topographical mapping between the location of the stimulus on the cortical surface and the location of the phophene in visual space. These experiments were subsequently replicated and extended to enable a blind volunteer to recognize Braille letters spelled out using sets of stimulation-evoked phosphenes (70,71). However, these early experiments also indicated that a prosthesis of only limited function could be produced with this technique because of interactions between phosphenes produced by different electrodes, flicker of phosphenes, and persistence of phosphenes following cessation of the stimulus, all attributed to the poor selectivity and large numbers of neurons activated by surface stimulation.

Therefore, an alternative approach, employing intracortical microstimulation with penetrating microelectrodes is being pursued. Fundamental studies on microstimulation of the human visual cortex (72) were conducted in three sighted volunteers undergoing surgery to remove epileptic foci. The results of these studies demonstrated that thresholds to evoke phosphenes were approximately two orders of magnitude lower for intracortical stimulation than for surface stimulation, and that phosphenes evoked by depth stimulation were steady, while surface evoked phosphenes tended to flicker. Further studies on intracortical microstimulation for restoration of vision were conducted using an array of 38 microelectrodes implanted in the cortex of a blind volunteer for four months (73). The results of these studies demonstrated that intracortical microstimulation produced small, constant phosphenes in an individual who was blind for 22 years. Further, intracortical electrodes separated by 500 μm could evoke distinct phosphenes, a significant advance in spatial selectivity as compared to surface stimulation.

An important element of a cortical visual prosthesis is a high-density microelectrode array suitable for chronic implantation in the brain. Several investigators have recently demonstrated high-density arrays of electrodes, fabricated from silicon using methods borrowed from integrated circuit manufacturing, which might be appropriate for creating a high-density interface with the visual cortex (74–76).

In addition to the ongoing work on a cortical visual prosthesis, there are also efforts to develop a retinal prosthesis (77). These devices are intended to be implanted on the inner surface of the retina and stimulate retinal ganglion cells (78) to restore vision in individuals who have intact retinal ganglion cells, but damaged or diseased receptors, for example, due to macular degeneration.

Electrocutaneous Stimulation

The visual and auditory prostheses described above used electrical stimulation to activate portions of the nervous system devoted to these functions, and therefore directly produce the sensations of sight or sound. In some conditions, however, damage to the nervous system is such that direct stimulation of the sensory neurons is either not possible or does not lead to sensory perception. For example, blindness caused by damage of the visual cortex cannot be addressed by stimulation of this compromised structure. In congenital blindness (where vision was never present), the usual development of the visual cortex may not occur and electrical stimuli applied there may not evoke sensations that can be interpreted in a visual manner. It may also be advantageous to provide an individual with information about the function of an artificial device, such as the grip force produced by a myoelectric artificial arm or the output commands from a hand-grasp neural prosthesis. In such cases, electrical (or mechanical) stimulation of tactile sensors in the skin has been investigated as a means to convey information about a different sensory modality, an approach called sensory substitution (79,80). Electrocutaneous stimulation (i.e., electrical stimulation of tactile sensors in the skin) in an area of the skin with intact sensation can be modulated by the variable of interest (e.g., grasp force) so that the user interprets the stimulation in terms of this variable rather than as tactile information. The information can be coded through single electrodes as changes in stimulus amplitude, stimulus timing, or both. Multiple electrodes can be activated progressively as the variable of interest changes, or arrays of electrodes can be used to provide information on inherently multidimensional modalities such as audition and vision.

Natural perception of tactile stimuli depend upon individual receptor properties, how the stimuli are spatially distributed across the skin, and how these stimuli change with time. Current systems for electrocutaneous stimulation do not activate receptors within this normal context, so individuals using this approach must learn to interpret the tactile information provided in terms of the modality of interest. This has proven to be problematic, and electrocutaneous stimulation has been successfully applied only to a few problems. Blamey and Clark (81) used electrocutaneous stimulation to provide auditory information to profoundly deaf individuals. Sabolich and Ortega (82) used electrocutaneous stimulation to provide center of pressure (a variable related to standing balance) feedback to individuals with artificial lower limbs. The Free-Hand hand-grasp neural prosthesis described previously is implemented with one stimulus channel, providing an electrocutaneous signal related to the user command signal.

Future work will likely focus upon the factors that have limited success to date. To maximize the transformation of tactile information into the modality being restored, stimulating electrodes must provide more consistent and repeatable inputs to the tactile system, perhaps by implantation. More closely spaced electrodes may allow the tactile system to be activated in a more natural spatial manner. Electrodes and stimulus parameters also need to be optimized to reduce the sensation of pain that often accompanies the tactile sensation produced by electrocutaneous stimulation.

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