GUEST EDITORIAL

Restoration of function: Current challenges and future opportunities through electrical stimulation

The early innovators in the field of functional electrical stimulation (FES) envisioned that function could be restored by the application of controlled electrical currents. Now, as a result of the support of agencies like the VA, NIH, and FDA, the first generation of clinical devices is available and used on a daily basis by individuals who have sustained central nervous system damage. In many cases, this is the first time that restoration of individual function has been possible.

What is available for people with disabilities? Devices are commercially available and have regulatory approval in the United States for restoration of hand function, bladder and bowel function, and respiratory control in spinal cord injury, suppression of seizures in epilepsy and tremors in Parkinson's disease, and audition for persons with hearing loss. Clinical research is ongoing in human subjects to restore standing and walking, swallowing, anal sphincter control, and for restoration of vision. Perhaps the early innovators could not have even dared to envision that individuals could so benefit by the procedures that they allowed themselves to dream about.

Why is it so attractive to consider the use of electrical stimulation for impacting disability? The answer to this question is actually quite simple, although the realization has proven to be harder to achieve. Electrical stimulation provides a means of activating or deactivating neural fibers and neural circuits in a selective and reversible way. This means that the effect can be localized. Furthermore, turning off the current may eliminate the effect. Alternatively, currents can be delivered in such a way as to make the effect longer lasting by taking advantage of the inherent plasticity of the nervous system. Next, the electrical stimulation is incredibly efficient. An extraordinarily small amount of current can generate enough muscle activation to lift the body. Electrical stimulation is also rapid acting, with the effect being observed in seconds.

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Finally, electrical stimulation can be applied safely. Methods for delivering current to biological tissue have been determined through careful science and testing. Safe stimulating waveforms that employ bi-directional pulses with charge densities below established limits are well tolerated by the tissue. Thus, electrical stimulation is an extraordinarily versatile, effective, and safe tool for manipulation of activity of the nervous system.

How does electrical stimulation help in maintaining and restoring function? Electrical stimulation impacts neural rehabilitation in

many ways and at different time scales. For example, in a neuroprosthetic device, stimulation generates the desired force and movement when applied, and the force generation ends when the stimulation is turned off. However, this stimulation can also result in longer-term changes in muscle physiology and chemistry, bone density, and spinal cord circuitry. The situation is similar in the cochlear implant, in which stimulation results in not only the generation of a percept but also in remodeling of the auditory system and in neuroprotection of the fibers of the auditory nerve. In deep brain stimulation, electrical stimulation appears to act by blocking the input from a dysfunctional circuit of the motor-control pathway. However, the effects of stimulation on tremor have a different time course than the effects on bradykinesia, which suggests different mechanisms are responsible. Thus, it is clear that electrical stimulation has multiple effects on the individual, several of which are incompletely understood at present. These are only a small number of clinical applications that you can envision if you consider the possibility of activating or deactivating neural fibers or neural circuits with the technology and knowledge yet to be developed.

What are the tools used to deliver electrical stimulation? The fundamental technology employed in these systems includes stimulators, electrodes, sensors, and the lead wires or communication channels that tie them together. The form of the technology is dependent upon the application. Generally, therapeutic effects can be achieved with short-term application of minimally invasive technology. Thus, skin surface electrodes or indwelling wires through the skin (so called percutaneous electrodes) are commonly used for these purposes. For neuroprosthetic applications, implanted technology is generally more appropriate since it will be used for a substantial period of the person's life, and the specificity and reliability afforded by implantation results in vastly improved function and convenience for the user.

Given this short overview, it should be obvious that it is impossible to generalize the current status of the field. However, some facts are readily apparent. First, functional electrical stimulation *works*, both as a therapeutic agent and as a neuroprosthetic intervention. This technology enables individuals with disabilities to regain personal control of their lives *now*. I am repeatedly overwhelmed by the impact the technology has. I have seen it enable a young mother to regain sufficient hand function to cook for her children or comb their hair; provide a young teacher with sufficient confidence in her bladder management to return to the classroom; allow a young woman to stand and sail at the helm of a boat; abolish unrelenting tremors and re-establish independence. However, more important than these types of anecdotal case reports are the results of the multi-center clinical trials that have proven this technology to be safe and effective. It works not only in one center that has the most advanced tools and support staff, it works in the clinic as a component of clinical practice. However, FES does not work for everything and for everyone, and proper candidate selection and proper application of the technology are essential if effectiveness is to be maximized. Next, the technology is deployable. Any number of clinician professionals, including both therapists and physicians, have developed the skills to effectively use this approach to help their patients. Its use is becoming widely integrated into clinical care (1). Third, FES systems are manufacturable. Neurological applications are predicted to be a major growth area for the medical device industry. Finally, it is reimbursable. This is a major hurdle for clinical acceptance, and third-party payers are finding the wisdom to understand that the long-term benefits of functional restoration offset the costs of purchase and deployment of the technology, as well as improve the quality of life (2,3).

What are the new tools that FES has to offer for the future? The major tool categories are sensors, electrodes, and stimulators, and the detailed "instruction set" of how to employ them. These tools are the integral elements of any system that is able to internally self-regulate. The instruction set allows us to predict how the tools will perform in various situations, through understanding of the mechanisms of action of these tools on the underlying neural tissue, and through modeling this performance.

Sensors that detect activity, such as physical movement, pressure, or electrical activity, may be used for control or feedback. Advances in microsensors and bioMEMS are likely to pay great dividends to our field. For example, triaxial accelerometers and micro-pressure transducers currently exist that are sufficiently small and low power to be implanted within the body. Next, impressive advances in electrode technology are making it possible to stimulate selected fascicles of a whole nerve, and to create unidirectional impulses on the nerve. This will make complete and selective activation of nerves possible, and open the possibility of inhibiting neural activity, for example to block spastic activity or pain. These electrodes also make it possible to record natural activity of afferent nerve fibers for feedback and control use. Even more impressive is the microelectrode development that will make possible the stimulation of spinal circuitry and cortical centers and selective recording from these regions. Complex high-density circuitry can be incorporated into the electrodes themselves, opening the possibility of directly accessing the central nervous system, and creating opportunities to interface directly with the neural circuitry that controls complex coordinated functions at the spinal or the cortical level. It also opens the opportunity for extracting control information from cortical neurons, such that intentions to move could be translated into signals that could be used to control movement. Finally, high-density stimulation and transmitting devices are under development; these will allow greater capacity to activate more channels of stimulation in a smaller volume, such as are envisioned by complex visual prostheses.

New technology will provide the tools for more precise interfaces to the damaged nervous system and will achieve even more significant clinical results. For example, in our Center alone, we have already made progress in this direction by showing that afferent signals recorded from the nerves innervating the bladder during filling could be used to help control bladder activity. In regard to the upper limb, clinical evaluation is underway on a neuroprosthesis for hand control that uses both implantable sensors and stimulators. This allows movement of the wrist to be translated into synergistic actions of the hand to supply grasp and release for persons with cervical-level spinal cord injury. The result is a natural control of the hand that is easy for the user to learn and eliminates much of the external hardware. Additionally, implementation of systems that provide more than one function are not far away. Of course, to utilize these tools effectively, and develop additional relevant tools, requires continued progress to understand the abnormal pathophysiology of neural injury, and how to interact with disordered control. With the maturation of the technology and its clinical introduction becoming more commonplace, such advances may be expected to grow, and with this the range of indications and number of individuals who will benefit will grow as well.

This is an extraordinarily exciting time of advancement. However, neuroprostheses are only one aspect of this story, and there are numerous examples of areas where combining approaches may ultimately provide the best effect. For example, the plasticity of the nervous system is being revealed in clinical trials for body weight-supported walking and constraint-induced arm therapy. We hypothesize that function improves because the remaining spinal and cortical circuits have the capacity to alter their function in an activity-dependent way that need not be driven only by the individual's remaining voluntary function, but also might be triggered or reinforced by an electrical stimulus. The FES provides a powerful set of tools, but they are not the only tools in the rehabilitation arsenal. We need to recognize that the totality of our intervention will be greater than the sum of its individual parts.

One can envision how the progress being made in many areas of basic science, biomedical engineering, and clinical practice might be brought to converge by the leaders in these fields. It is clear that the rehabilitation of an individual with a disability is accomplished using many modalities contributed through the expertise of numerous specialists working in concert. As new tools are discovered and demonstrated to be safe, they are added to the practitioner's armamentarium. Another area of possible convergence of new tools and techniques is related

to neural regeneration. Hopes and expectations for regeneration are high, and laboratory research results are reason for cautious enthusiasm. But there are still many unresolved questions that might be best answered by combining biological approaches with other techniques such as FES. For example, we know that activity affects the growth of the regenerating axon. It is not unreasonable to expect that electrical stimulation could be used to enhance this effect. Another related area is tissue engineering, which is continually developing more exciting means of directing growth in all types of tissue, including nerve tissue. Another opportunity for convergence is to figure out how to take advantage of partial connectivity that might result from incomplete or nonspecific regenerative processes. This is an obvious area where neuroprosthetics can contribute by amplifying small signals to create larger actions and by inhibiting undesired activity.

Where must we focus attention in order to achieve such accomplishments? Certainly each of the contributing methodologies must continue its development and demonstrate its effectiveness. For this to occur, continued discovery must be supported. In the United States, we are fortunate to have the VA and the NIH as committed partners in pursuing this knowledge creation and technology development. Creativity must be rewarded. It must become easier for scientists to pursue the more risky directions of science that could pay larger dividends. We must be sure that the best young and uninhibited minds are attracted and fully equipped to tackle such difficult problems. They must have the right training, with knowledge of how to work together across disciplines, without barriers. We must set an example to help them understand that a single magic bullet does not exist, and that "the solution" to the complex problems experienced in CNS dysfunction is more likely to be a combination of approaches that we have yet to imagine. It is up to us to break the barriers that separate us and encourage a real collaborative attack on our common problems. It is understanding how to combine approaches at the right strategic times that will optimize our attack to accomplish the most optimal restitution of function. We must find the ways to continue to converge ideas and approaches offered by basic scientists, applied scientists and engineers, clinicians, and the users such that the science can be made clinically relevant and that new, trans-disciplinary treatments are incorporated as the standard of clinical care.

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For additional information contact the Cleveland FES Center or Cleveland FES Information Center at http://www.fesc.org.