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Challenges and Opportunities in Restoring Function after Paralysis

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Abstract

Neurotechnology has made major advances in development of interfaces to the nervous system that restore function in paralytic disorders. These advances enable both restoration of voluntary function and activation of paralyzed muscles to reanimate movement. The technologies used in each case are different, with external surface stimulation or percutaneous stimulation generally used for restoration of voluntary function, and implanted stimulators generally used for neuroprosthetic restoration. The opportunity to restore function through neuroplasticity has demonstrated significant advances in cases where there are retained neural circuits after the injury, such as spinal cord injury and stroke. In cases where there is a complete loss of voluntary neural control, neural prostheses have demonstrated the capacity to restore movement, control of the bladder and bowel, and respiration and cough. The focus of most clinical studies has been primarily toward activation of paralyzed nerves, but advances in inhibition of neural activity provides additional means of addressing the paralytic complications of pain and spasticity, and these techniques are now reaching the clinic. Future clinical advances necessitate having a better understanding of the underlying mechanisms, and having more precise neural interfaces that will ultimately allow individual nerve fibers or groups of nerve fibers to be controlled with specificity and reliability. While electrical currents have been the primary means of interfacing to the nervous system to date, optical and magnetic techniques under development are beginning to reach the clinic, and provide great opportunity. Ultimately, techniques that combine approaches are likely to be the most effective means for restoring function, for example combining regeneration and neural plasticity to maximize voluntary activity, combined with neural prostheses to augment the voluntary activity to functional levels of performance. It is a substantial challenge to bring any of these techniques through clinical trials, but as each of the individual techniques is sufficiently developed to reach the clinic, these present great opportunities for enabling patients with paralytic disorders to achieve substantial independence and restore their quality of life.

Index Terms

Functional restoration; Neural prostheses (Neuroprostheses); Paralysis

I. Introduction

There are an estimated 5.5 million people in the United States living with paralysis. This estimate defines paralysis as a central nervous system disorder resulting in difficulty or inability to move the upper or lower extremities. These numbers, analyzed by the Christopher and Dana Reeve Foundation, include approximately 1.6 million people who are stroke survivors, over 900,000 people with Multiple Sclerosis, over 400,000 with Cerebral Palsy, and 1.2 million people who have sustained spinal cord injury (SCI) [1].

The impact of the body systems affected by paralysis is enormous, as virtually all body systems can be affected. This includes upper extremities, lower extremities, trunk, bowel, bladder, sexual function, breathing, and sensation. Paralysis often affects multiple body systems in a single person, and the result of this paralysis has a significant impact on their independence and quality of life. The manifestations of paralysis include loss of voluntary movement, undesired movements such as spasticity and spasm, loss of sensation leading to skin breakdown and loss of perception, and pain. Not surprisingly the functional recovery desired by people with spinal cord injury is related to restoring functions lost as a result of paralysis. In an excellent study performed by Anderson [2], a population of people with spinal cord injury was asked to identify their highest priority for functional recovery. The population was divided into people with tetraplegia, or four-limb involvement, and paraplegia, or two-limb involvement. For people with tetraplegia, the overwhelming greatest desire was restoration of hand and arm function, with sexual function, trunk stability and bladder and bowel function rated next highly. For people with paraplegia, sexual function, bowel and bladder function, walking function and elimination of chronic pain were the most highly ranked. Not surprisingly, people with spinal cord injury are not looking to have just one of these functions restored, but all of them. Thus, a grand challenge is to develop means for restoring function including both movement and sensation, and elimination of pain for people with paralysis. While this paper will focus on spinal injury, these comments can be generalized toward other disability groups who have been impacted by paralysis.

There are alternative treatment options for people with paralysis, the most common being therapy and medical management, the use of assistive technology such as orthotics or braces, and mobility aids such as wheelchairs, cushions, urinary collection devices, etc. More recently, restorative therapies such as body weight supported treadmill training have been investigated to restore latent circuits in the spinal cord that could be “awakened” through the repetitive movement. Surgical interventions are few but include tendon transfers and, in some cases, full muscle transfers. These treatment options can provide a significant functional gain for select individuals. However, these alternatives leave significant gaps in the needs for functional restoration. Restoration is nearly always far from complete and leaves the individual with considerable functional loss, often necessitating human assistance for major daily activities. The challenge is to deliver meaningful solutions that are integrated into the daily life of the user and enhance their independence and quality of life. Novel technologies that interface with the nervous system play a critical role in addressing this need.

Electrical stimulation, as either a therapeutic intervention to restore latent circuits or a neuroprosthetic intervention to substitute for the paralysis by electrically activating the neural tissue below the level of injury, has been extensively evaluated. Functional electrical stimulation (FES) has been shown to provide functional gains beyond those that can be achieved by any other means. Finally, neural regeneration, a biological approach, has been extensively researched, but has yet to provide an impact in restoring function. Looking forward, there is a significant opportunity to consider hybrid approaches that combine functional recovery and functional restoration. Such hybrid approaches would seek to maximize recovery of voluntary function, and couple that recovery with substitution approaches, such as neuroprosthetics, in order to achieve full functional restoration.

There are significant challenges that are associated with each of these approaches, not only in the execution of them individually, but from the clinical perspective. For example, some disorders such as spinal cord injury are orphan diseases in which a relatively small number of patients are impacted. However the magnitude of the impact creates enormous societal costs since the individual will be affected for many decades of their lives. In addition, the injuries are heterogeneous and one solution does not necessarily apply to all individuals. Finally, clinical dogma used today suggests that early treatment should not include invasive procedures, yet these procedures are likely to be more effective when utilized soon after injury, before further co-morbid conditions arise. These changes include muscle atrophy, contractures of joints, spasticity, and overall limb weakness that accompanies disuse and progresses with time after injury. There are also significant technical and scientific challenges. Technology is expensive, particularly class III medical devices. In many cases the appropriate devices do not exist, or, if they do, they are inaccessible for clinical trials in off-label applications.

II. Technology

Electrical stimulation plays an important role in addressing the challenge of restoring function in paralytic disorders. The specific role depends on the mode of delivery of the electrical stimulation, which can be via surface, percutaneous or implanted electrodes. The delivery of electrical stimulation via surface electrodes includes applications such as biofeedback or FES cycling. With surface stimulation, electrodes are placed on the skin to temporarily cause contraction of the underlying muscles. Percutaneous stimulation, where a percutaneous lead is inserted through the skin and connected to an external stimulator, can be used for temporary treatments or as a demonstration phase prior to development of more permanent approaches. The neuroprosthetic approach, which includes a partially or fully implanted device, is intended to provide long-term functional restoration. Neuroprostheses utilize a surgically implanted pulse generator which is connected to an array of electrodes with custom programming capability to control and activate the generator.

Within the “toolkit” of restoring function for people with paralysis, there are largely two primary tools, both of which are needed. The first is the electrodes. Surface electrodes are the most common, with at least tens of thousands in use for many different clinical applications. Surface stimulation is commonly used in applications such as biofeedback, FES cycling, and TENS (transcutaneous electrical neural stimulation) applications in which

electrodes are placed to generate a temporary contraction of a muscle. Percutaneous electrodes have been used for decades in clinical feasibility studies [3] and now are in pivotal clinical trials. Percutaneous stimulation is generally for a temporary demonstration phase, in which an electrode is introduced through the skin and connected to an external stimulator. Percutaneous electrodes have been approved for long-term implantation to provide respiratory control in SCI and ALS patients, as reviewed below [18]. The performance of these electrodes is very good, but advances in new materials offers an approach in improving the performance even further. However, at present percutaneous electrodes are used primarily for short term testing.

Implanted neuroprostheses utilize many styles of electrodes based on the targeted neural structures (Fig 1). Intramuscular or epimysial electrodes, which are placed in or on the muscles to be activated, have been used in the thousands, and have demonstrated excellent performance [4,5]. Nerve electrodes, which are placed around or adjacent to nerves, include several designs, many of which are in clinical use commercially. Nerve electrode design is continuing to evolve, particularly with respect to designs that have multiple contacts for activating specific targeted portions of a nerve.

There are also spinal cord epidural stimulators, thousands of which are in clinical use particularly for spinal cord stimulation, and those electrodes, or a variance of them, have been used by researchers such as Harkema [6] for stimulation of the spinal cord for restoring motor function, and DiMarco [7] for stimulation of the spinal cord for producing cough. Finally, there are intraspinal microstimulation electrodes, designed to be inserted within the spinal cord or peripheral nerves, which are currently in preclinical studies. The substantial challenge that these implanted electrode technologies must meet is the increasing demand for more selectivity of nerve activation, toward the individual nerve fiber level, which will enable the full complement of motor and sensory fibers to be controlled. These new electrodes must be deployable into the operating theater and provide a stable response and reliable performance over decades of use.

The second primary component of the toolkit is the stimulator (or IPG – implanted pulse generator), which is linked to each electrode to deliver electrical current for activation. As with electrodes, a variety of stimulator designs exist. For surface electrodes, there are many stimulator designs available, most of which operate open-loop. For percutaneous electrodes, there are new low-profile designs that are currently being used in pivotal trials [8]. Implanted stimulators can be categorized according to the manner in which they are powered. Most implanted stimulators for treatment of paralysis are inductively powered, although some are battery powered using either primary or secondary cells. Most implanted stimulators have only one or two channels of stimulation. Although designs exist for cochlear stimulation with 22 channels and visual prostheses with 60 channels, these devices develop one to two orders of magnitude less stimulus amplitude and charge, which is insufficient for neuromuscular applications. Some of these devices are programmable, but almost all existing stimulators operate in an open-loop fashion. There are emerging designs, one of which is a modular neuroprosthesis that can be used to create a scalable implanted network within the body [9], as shown in Figure 2 and discussed below. This type of system is advantageous for deploying to people with spinal cord injury since it conceptually can be

tailored to activate or inhibit neural structures in many different areas of the body, and thus has the potential to provide multiple functions for a single individual.

In summary, there are many implant designs, but many of these are not generally available at present. Most implantable pulse generators are designed for specific indications, and most are not available for use beyond their specifically designed application. For the implementation of new designs, there is a good stable of subcontract manufacturers with capabilities that encompass all of those needed to produce sophisticated implanted devices. The evolving tools will provide a platform technology for new clinical discovery and application. It must always be remembered that there will be a need to design the entire system, not just the individual components, so that electrodes and leads can be deployed within the operating theatre by a means which is consistent with current or evolving surgical practice and these can be upgraded or fixed in the event of a failure.

III. Clinical applications

There are many major unsolved clinical problems associated with paralysis. These include restoring movement, providing command control inputs, restoring sensation, suppressing spasticity, and controlling pain. The technology described above is useful in addressing these major unsolved clinical problems, but the delivery of the technology must be matched with the particular indication. Some examples offered below demonstrate the impact of electrical stimulation in overcoming some limitations of paralysis.

A. Retraining and Neural Plasticity

Work of Knutson and Chae [10] is demonstrating that reorganization of the nervous system is possible following chronic stroke. In their work, a conceptually simple surface stimulation technique is used, in which the non-paralyzed arm is fit with a sensor to record voluntary movement and the opposite affected limb is fit with surface electrodes to activate the paralyzed muscles (Fig 3). Through a translational algorithm, when the unaffected arm moves and the hand is opened, the opposite hand is stimulated and opens as well in a mirroring program. This technique has been demonstrated in feasibility studies with stroke patients, and early results indicate that the speed of recovery is faster with stimulation.

This rather straightforward approach demonstrates a possible means for restoration of function, which is reorganization of the central nervous system through induced activity. Thus activity is likely to be an important ingredient in functional restoration, as is voluntary effort. Greater knowledge about neural plasticity must be acquired and techniques must be developed in order to deliver such principles into the clinic to achieve meaningful clinical impact.

A second example of the impact of electrical stimulation has been recently demonstrated by Moritz [11]. This work shows the potential effect of therapeutic intraspinal stimulation on recovery of a spinal cord contusion injury in pre-clinical studies (Fig 4). Four weeks after an induced contusion injury to the surface of the spinal cord of rats, intraspinal microstimulation was applied, seven hours a day, five days a week. The animal was scored

in the use of their forepaw during recovery. Reaching success was significantly enhanced in the rats who received intraspinal microstimulation relative to the unstimulated rats.

This demonstrates another possible example of neural plasticity in early post-injury intervention. This paradigm, if transferrable to human subjects, could result in improved use of function of the hands. It also brings up many translational questions. Could this intervention be applied early after spinal injury, and how early? Will the electrodes be stable for the period of time, and would they have to be removed if recovery was sufficient? Is the recovery of function maintained following stimulation, etc.? Nevertheless, these experiments provide a window into the opportunity for an early intervention that could be useful in restoring active movement after spinal cord injury.

The work of Harkema and Edgerton et al., has demonstrated an intervention using epidural spinal stimulation below the level of injury in human subjects [6]. This work follows extensive studies in rats by Edgerton and colleagues, where apparently synaptic conductivity could be influenced by epidural spinal stimulation. This work applied to a human subject with a clinically complete spinal cord injury has been reported to provide some ability to stand, some bladder and bowel changes, and limited movement of the legs. A similar result was demonstrated by Carhart, et al., in incomplete injury [12]. These results demonstrate that synaptic connections below the spinal injury can be altered with electrical stimulation and may enhance function. These examples provide a window into the future for restoration of function following paralysis by activating latent circuits of the spinal cord.

B. Suppression of Spasticity and Pain

Electrical currents can also be used for blocking neural activity. Kilgore and Bhadra [20] have shown that high frequency stimulation on the order of 10 kHz can be used to block the conduction of action potentials along a peripheral nerve, as shown in Fig. 5. While most clinical applications utilize activation of nerves for restoring function, many clinical problems are associated with hyperactivity of the nervous system. Control of pain and spasticity are two possible areas that could benefit from suppression of neural activity. Applications in spasticity control could be applicable to patients with stroke, Multiple Sclerosis and Cerebral Palsy, for bladder and bowel sphincter relaxation, relieving contractures due to over-activity, and numerous other indications. Thus, this new foci toward blocking neural activity provides an additional approach for restoring function in paralysis. This technique is currently being explored for use in pain control (Neuros Medical, LLC, Willoughby, OH).

C. Neuroprostheses

Another approach that is achieving clinical success is implanted neuroprostheses. These are being used to provide standing and walking, grasp and arm function, bladder control, and respiratory control.

Standing and Walking—Standing and walking with percutaneous neuroprostheses has been pioneered by Marsolais and Kobetic [13] in the 1970's and has now progressed to standing and transfer systems, and walking systems with implanted neuroprostheses. This

work, now led by Triolo, et al [14] has demonstrated that with peripheral stimulation of the paralyzed nerves and muscles of the lower extremity, activation of individual muscles can be coordinated together into standing and walking patterns which enable ambulation by the user. Such systems, which began through the use of percutaneous electrodes, have now progressed to implanted devices with up to 24 channels of stimulation.

The implanted device uses a transcutaneous radiofrequency link to supply power and control of the implanted stimulator, as shown in Fig. 6. The subject uses an external toggle switch to control the desired movement trajectory of the limb for standing, stepping, etc. Often, intramuscular and epimysial electrodes have been used, but more recently the investigators have utilized nerve cuff electrodes which encircle the nerve for stimulation of a greater number of nerve fibers and therefore muscle fibers. These neuroprostheses have been implanted in the legs of 50 paraplegic spinal cord injured and stroke patients.

For standing and transfer functions, which are critical in the lives of people with paralysis and relieve care givers of considerable effort, many of the challenges have been met and a small multi-center clinical trial has been completed. Sufficient joint torques at the hips and knees can be generated that enable assisted standing and moving from one seated posture to another with minimal assistance from an attendant. These provide significant function, and require only minimal external hardware. However, postural control is limited and support of at least one hand is required. For walking, there remain many challenges to overcome. It is not always possible to produce sufficient torques at all joints and some muscles may have insufficient endurance. Systems are largely open loop, and require significant concentration of the user. Most walking is over even terrain, and limited studies have been performed up and down stairs and ramps. While function is impressive in the relatively small numbers of subjects with complete paraplegia who have been studied, the clinical goal of hands free walking is a significant challenge. It is most likely that advances that would be the most viable approach will address patients with incomplete injuries and the major challenges that are unmet by current technologies, such as external orthotics and wheelchairs to achieve walking for limited duration in confined spaces and up and down surfaces.

Upper Extremity—Another indication for implanted neuroprostheses is for restoration of hand and arm function for individuals with cervical level spinal cord injury. This work utilizes an implantable stimulator sensor device with 12 channels of stimulation and two channels for sensing myoelectric activity, as shown in Fig 7.

The myoelectric activity is used to select the grasping configuration of the hand and to proportionally control opening and closing of the hand [15]. The 12 channels of stimulation are used to activate the paralyzed muscles necessary to provide grasp opening and closing, wrist movement, forearm movement, and elbow extension. This system has been fitted on 13 people with cervical tetraplegia, including four persons bilaterally. An earlier system, called FreehandTM, was implanted world-wide in approximately 250 people with spinal cord injury and received pre-market approval from the FDA, but is no longer on the market. These systems have demonstrated safety, efficacy, and clinical utility for these patients. Addressing the deployment challenges presented by an orphan population is discussed below.

There remain significant challenges that can improve the functionality of upper extremity systems. First, only a finite number of basic “grasping patterns” are provided for major functional tasks. While these enable users to achieve major activities of daily living, they fall short of the remarkable dexterity of the hand of able-bodied individuals. A major reason for this is due to the limited command control information that is available, with generally only two or three independent control sites being available. Availability of more robust control methods would allow more dexterous grasp to be provided with finer digital control. Such control methods could include advanced brain control interfaces [21]. If such control methods were available, better internal control of the digits would most likely be required. This would necessitate closed-loop control of movement, and development and integration of sensors into the neural prosthesis. Most patients with cervical SCI also have lost sensation in the extremity, meaning that the user has to rely on visual input for interpretation of hand performance. Advanced techniques for restoring sensation, as discussed below, are required. Additionally, addressing the issues of high level tetraplegia remains a significant challenge. In this case, control not only involves the hand, but also placement of the arm through space with considerable accuracy. In most high level SCI, patients also present with denervation of muscles due to the involvement of the anterior horn cells in the spinal cord. Restoring function via these muscles will require developing means of creating axonal growth into the denervated muscles, or using hybrid systems of orthotics and electrical stimulation.

Many additional critical body functions can be impacted through neural interfaces. These include systems that enable control of urinary and fecal incontinence, respiratory functions, and sensation. While substantial clinical progress has been made, there are also great unmet needs.

Bladder and Bowel Control—Bladder control systems have been pioneered by Brindley, and there are currently more than 3000 systems being used today by people with SCI [16]. This device uses stimulation of two or three sacral roots to provide controlled voiding in spurts. Bladder contraction is provided by stimulating the smooth muscle of the bladder wall, which simultaneously activates the external sphincter (ES), a skeletal muscle. Cessation of stimulation allows the ES to relax quickly and the remaining pressure in the bladder to expel urine. This sequence is repeated for several cycles, until residual urine is small. The primary clinical problem with this system is that frequently a dorsal rhizotomy is needed to allow urine passage, which is irreversible and has many unacceptable side consequences, including loss of erectile function. Current research investigating sensory afferent pathways to relax the ES or temporary high frequency block, discussed above, might allow a means for implementation of this system without rhizotomy.

Respiration and Cough—Respiration and cough has been provided by implanted neuroprostheses. Glenn et al [17] pioneered the use of phrenic nerve stimulation to supply respiration for people with high level SCI. This required an extensive operation, and has not been widely accepted clinically. Onders et al [18] have developed a minimally invasive means for implantation of percutaneous electrodes into the diaphragm, significantly reducing surgical complexity. This system can supply 24/7 breathing and eliminate the need for a respirator. As well, patients can smell, as air is passed through the olfactory sensors,

providing a quality of life advance to people with high level SCI. It has received a Humanitarian Device Exemption from the US FDA, and has been implanted in more than 400 patients with SCI and amyotrophic lateral sclerosis (ALS). This system is implemented with percutaneous electrodes, which have demonstrated excellent performance. However, the percutaneous site still requires maintenance, and linking this system to an implanted stimulator remains a possibility.

The inability to cough and clear the airway can cause major complications for people with SCI. DiMarco et al [7] have demonstrated that epidural stimulation of the dorsal spinal cord at the lower thoracic segments can generate significant expulsion of air and airway clearance. This system has been implemented in 17 people with SCI, who have been using this system for as long as seven years. The primary challenge for this system involves simplifying the surgical installation, potentially through the use of linear-style electrodes that do not require laminectomy for implantation on the dorsal spinal cord.

Restoration of Sensation—Restoration of sensation is another significant challenge for people with paralysis and limb loss. Failure to have sensation is reported to lead to falls, skin ulceration, and burns. Tyler et al [19] have demonstrated restored percepts in the hand areas using 19 channels of stimulation with nerve cuff electrodes placed on the radial, median and ulnar nerve in amputees. Each of the 19 electrodes provided sensation in unique locations in various regions of the volar and dorsal hand, including fingertips, thumb tip, thenar eminence on the volar side and thumb, wrist and hand on the dorsum, as shown in Fig. 8.

This technique provides a window of understanding regarding how sensation could be supplied to amputees through a sensory feedback system utilizing a multichannel implanted cuff system.

IV. Challenges for the future

The technologies that will be required to address the complex challenges of paralysis must be far advanced from those that are on the market today. Because most persons with paralysis have a multi-functional loss, the tools must be made available to address these multiple clinical problems. Thus, the design of neuroprosthetic systems has evolved to meet the needs presented by multi-functional loss. One approach being utilized by our team is a single implantable system composed of intercommunicating modules which can be distributed throughout the body to supply the local delivery of electrical current or for the recording of biopotential signals (Fig. 2).

Electrodes for either stimulation or inhibition of neural activity could be placed on the desired nerves or muscles. Such a system is modular and can consist of a number of individual modules that can be configured to meet the clinical need. Furthermore, because rechargeable batteries have developed with significant capacity and can be discharged and recharged for multiple cycles, the design of a fully implantable system now becomes practical for a multiple function system, enabling the patient to be freed of any cumbersome external components of the system.

While this paper has focused primarily on electrical activation, there are other techniques that interface with the nervous system as well. Electrical activation is the most advanced and the most proven, and it has been demonstrated that it can be delivered safely, reversibly, and precisely to nerves or nerve populations, but not at the cellular level. Drugs provide another means of pharmacologically interfacing the nervous system. At present, intrathecal delivery is a systemic technique that can be used to alter nerve activity for spasticity control, but techniques for more precise and specified delivery to neural targets are needed. Two additional techniques are magnetic stimulation and optical stimulation. Magnetic stimulation utilizes magnetic fields delivered to the tissue from outside the body, and improvements in this technique have demonstrated improved specificity of the area of stimulus generation. Continued evolution of this technique is expected. Another evolving technique is optogenetic stimulation, in which neural fibers are virally infected with light responsive elements which then respond specifically when the appropriate color of light is delivered to the neural tissue. This technique is attractive because it offers the possibility of considerable specificity. For this technique to be clinically viable, considerably greater scientific knowledge and engineering development is required to design devices that can achieve regulatory approval.

Longer term challenges remain in restoration of function after paralysis. New interfaces that enable specificity of activation of fibers of the peripheral nerve at the cellular level could be used in advanced systems. Advanced neuroprostheses are also likely to employ closed-loop feedback control and thus will require a sensing and delivery system. This will require the development of new sensors that do not exist today. Considerable work is on-going to develop cortical interfaces that provide “natural but generated control” such as discussed by Dr. Gao in this issue [21]. Whether these systems need to be externalized or implanted remains to be investigated and considerable activity ongoing around the world has demonstrated the potential for this method to enable people with paralysis to communicate and control their assistive technology and neural devices. Regeneration of nerve fibers remains a goal for restoration of function after paralysis. Tissue engineered scaffolds that direct regeneration and provide structures for growth are likely to be an important contribution for neural regeneration. Such techniques are currently in development by several laboratories.

It is likely that as new approaches are successful in achieving clinical approvals, combinatorial strategies involving hybrid systems will ultimately be most important in restoring function. Techniques that can enhance synaptic inactivity, provide artificial activation of nerve fibers or nerve cellular networks, and regenerative strategies using scaffolds and pharmacological techniques ultimately will most likely be brought together to address the enormously complex problems of paralysis. A hybrid approach is often used at present in neuroprostheses, with tendon transfers of muscles that are paralyzed but can be stimulated used to substitute for denervated muscles. The additional function that may be achieved as additional techniques reach the clinic provides a framework to envision the future of functional restoration in paralysis.

The challenges for the future lie not only in the technological challenges that will address the multiple problems presented by paralysis, but to deploy these as systems into the health

care system. New technologies must be cost effective in addressing the health needs of the user, and outcomes must demonstrate not only safety and functionality in their use, but the overall benefits that are derived. For persons with paralysis whose lives can be significantly improved by their ability to control their bladder, eat independently, and breathe on their own, these measures should be self-evident, and data that demonstrates this must be developed. There are particular challenges for the new products to reach the market for some “orphan” populations where there is a small population who have a particular disorder, such as spinal cord injury. This is because the market drive is small relative to the costs associated with the clinical trials and sustaining the product on the market. For such new technologies, innovative approaches must be taken. One such approach is demonstrated by the Institute for Functional Restoration at Case Western Reserve University (<http://casemed.case.edu/ifr/>) where the university is facilitating the pivotal trials through a non-profit model.

In summary, the repercussions of paralysis are enormous, both personally to the individual and to their family; and have huge costs to society. Paralysis can take many forms with multiple disorders causing paralysis. Within individual groups of patients there is a heterogeneity of the injury which presents a challenge in development and deployment of tools for restoring function. These tools are emerging and safety is proven for many systems. There are opportunities for both recovery of function and restoration of function, and these must be brought together to maximize the capabilities gained by the individual. There are several examples of successful deployment in the clinic, and clinicians desire them and patients will accept these solutions. There must be a trained workforce that understands these systems, both for development and for future translation to the clinic. As we see these innovative translational approaches reaching the clinic, there will be a realization by the patients of the multiple clinical benefits that they provide to their lives.

V. Summary and Conclusions

The repercussions of paralysis are enormous, both personally to the individual and to their family; and have huge economic costs to society. Paralysis takes many forms with multiple disorders causing paralysis, and multiple body systems often affected. Within individual groups of patients there is heterogeneity in the injury which presents a challenge in development and deployment of tools for restoring function. Many of these tools are emerging and safety is proven for some systems. The unmet clinical needs are substantial, and there are opportunities for both recovery of function by enabling body systems to regain voluntary function, and for restoration of function with permanently implanted neuroprostheses.

There are many areas that represent opportunities for future discovery. The technologies of tomorrow must allow activation and inhibition of nerve fibers at the axonal level. To do so will require advanced neural interfaces with greater selectivity than is presently available, and implantable generators which have flexibility in their configuration to address the broad range of paralytic disorders. These interfaces must be deployable into the clinic, and assessment of their performance must demonstrate a substantially improved function, independence, and quality of life for the users.

Many body systems can be affected by neurotechnologies, including movement of the extremities, respiration, bladder and bowel control, sensation, pain suppression, and spasticity. While some systems have been brought through clinical trials, the number of patients impacted today is relatively small. Some of reasons include unavailability of suitable technology, insufficient performance, difficulty in clinical deployment, and the cost relative to the reimbursement, all of which represent opportunities for new advancements. Deployment through pivotal trials represents a significant challenge, with orphan populations often involved, and models for achieving regulatory approval in this environment is challenging. As we see these innovative translational approaches reaching the clinic, there will be a realization by the patients of the multiple clinical benefits that they provide to their lives.

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Biographies

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He is the Donnell Institute Professor of Biomedical Engineering and Distinguished University Professor at Case Western Reserve University. He is also Senior Research Career Scientist at the Louis Stokes Cleveland Veterans Affairs Medical Center and former director of the Functional Electrical Stimulation Center of Excellence. His research interests include neural engineering and neuroprostheses and translational research. As Executive Director of the Institute for Functional Restoration, he is working to insure that advances in rehabilitation technologies are sustainably deployed into the clinic.

Kevin L. Kilgore received his B.S. degree in Biomedical Engineering from the University of Iowa and his M.S. and Ph.D. degrees in Biomedical Engineering at Case Western Reserve University. Dr. Kilgore currently serves as Program Manager in the Department of Orthopaedics at MetroHealth Medical Center, where he directs research and clinical applications. He is a Clinical Instructor at Case Western Reserve University School of Medicine and Adjunct Assistant Professor in the Dept. Biomedical Engineering at Case Western Reserve University; Associate Director, Cleveland FES Center; and Biomedical Engineer, Department of Veterans Affairs. Dr. Kilgore's primary research interest is in the application of functional electrical stimulation (FES) and neuroprostheses to provide disabled individuals with increased independence and improved quality of life.

Fig. 1. Various implanted electrodes used with neuroprostheses. These electrodes all stimulate nerve fibers and cause activation or inactivation of the nerve, depending upon the stimulus waveform that is used. Electrodes can also be used for recording of signals from nerve or muscle.

Fig. 2.

An advanced neuroprosthesis consisting of distributed modules. Left: This networked neuroprosthesis has modules for power, stimulus delivery and for recording physiological or physical activity, network cabling and electrodes. This system is fully implanted, and can be externally programmed and/or controlled in real time. Right: Networked neuroprosthesis as configured for an upper extremity system for spinal cord injury. Each module can be placed close to the site of stimulation or recording.

Fig. 3. Mirroring system for stroke survivors. The subject wears a sensor glove on the unaffected limb, and surface electrodes on the affected limb. Intention on the unaffected limb generates stimulation to the affected limb, allowing tasks to be performed. This relatively simple concept has demonstrated one manifestation of using neural plasticity for recovery of function. Work of Knutson and Chae [10].

Fig. 4.

Intraspinal microstimulation (ISMS) delivered after spinal cord contusion demonstrates improved reaching capabilities in rats. Transfer of this technique to humans is a considerable way off, but demonstrates another opportunity for altering neural circuitry after spinal cord injury. Work of Kasten, Sunshine, and Moritz [11].

Fig. 5.

High frequency currents may be used to block neural activity. Applications include blocking painful sensations and spasticity, or undesired muscle contraction, in disorders that are wide ranging and include stroke, amputation, spinal cord injury, cerebral palsy, and multiple sclerosis. With the application of current in this animal model, neural firing is suppressed for the duration of the stimulus block and reversed quickly upon cessation of the blocking current. Work of Bhadra and Kilgore [20].

FES Walking System

Fig. 6.

Walking system with an implanted neuroprosthesis. Stimulation and coordination of multiple muscles together is provided by the neuroprosthesis. Individual muscle actions are stimulated by implanted intramuscular or nerve cuff electrodes, and coordination of the actions are programmed into the external controller. Communication between the controller and implanted stimulators is via radio frequency signals. Control is provided by an external switch. Work of Triolo, Anderson, and Hoen [14].

Implanted Stimulator Telemeter System

Fig. 7.

Implanted neuroprosthesis for the upper extremity in spinal cord injured patients. A similar technological implementation as the lower extremity, but control is more intimate and is provided by myoelectric signals from muscles that retain voluntary control. Bilateral systems have been developed. Work of Kilgore, Keith, Hoyen, and Peckham [15].

Fig. 8.

Restoring sensation has been a significant unmet challenge in the case of paralysis and limb loss. Newer technology that provides selective stimulation of individual fascicles of nerves may be a means of generating percepts distributed to areas of the lost limb. Areas of sensory perception in the hand from nerve electrodes are shown in one amputee subject. Work of Tyler, Schieffer, Tan, Keith and Anderson [19].