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REVIEW: Sir Ludwig Guttmann Lecture

Functional electrical stimulation after spinal cord injury: current use, therapeutic effects and future directions

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Repair of the injured spinal cord by regeneration therapy remains an elusive goal. In contrast, progress in medical care and rehabilitation has resulted in improved health and function of persons with spinal cord injury (SCI). In the absence of a cure, raising the level of achievable function in mobility and self-care will first and foremost depend on creative use of the rapidly advancing technology that has been so widely applied in our society. Building on achievements in microelectronics, microprocessing and neuroscience, rehabilitation medicine scientists have succeeded in developing functional electrical stimulation (FES) systems that enable certain individuals with SCI to use their paralyzed hands, arms, trunk, legs and diaphragm for functional purposes and gain a degree of control over bladder and bowel evacuation. This review presents an overview of the progress made, describes the current challenges and suggests ways to improve further FES systems and make these more widely available.
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Introduction

The foundations for modern management of spinal cord injury (SCI) were created more than half a century ago by the pioneering work of Dr Donald Munro in the United States and by Sir Ludwig Guttmann in the United Kingdom. Munro opened the first SCI unit, but Guttmann created the first comprehensive SCI center for medical and rehabilitation care. Under his strong leadership the care of persons with SCI was completely changed.

I was lucky enough to meet Sir Ludwig once in person. It was in the late 1970s at a meeting in New York City. He clearly was a man of great energy and self-confidence, who addressed my question to him with interest. At that time, I was involved in research relating to the neuroendocrinology of persons with SCI, especially production of catecholamines during episodes of autonomic dysreflexia. Most descriptions of the clinical symptoms of autonomic dysreflexia at that time stated that there was increased sweating above the level of the cord lesion. For example, one textbook contained the following statement: 'In complete lesions the lack of thermoregulatory sweating below the level of injury is often associated with excessive diaphoresis above the level of injury'.[1] Because sweating is controlled by the sympathetic nervous system which has all its efferent nerve fibers exiting from the thoracic cord, I had difficulty understanding which autonomic nerves control sweating of the head and neck 'above the level of injury'. Sir Ludwig pointed out to me that sweating of the head and neck was not a thermal regulatory response in persons with tetraplegia and was generated by activity of the sympathetic nerves below the level of the lesion. In other words, sweating of the head and neck was a below level phenomenon and it was wrong to state that excessive sweating in autonomic dysreflexia occurred above the cord lesion in persons with tetraplegia.

Based on the work of Sir Ludwig Guttmann, specialized SCI medical care and comprehensive rehabilitation has focused on securing good health and maximum function in mobility and self-care compatible with the neurological condition, as well as to help each person with SCI to return to the community and to achieve high quality of life. Much has been accomplished by this approach. Life expectancy of people with SCI has increased every year since the 1940s. Morbidity, that is, medical complications, has decreased and consequently people with SCI have needed shorter initial hospital length of stay[2] and fewer rehospitalizations.[3] Many medical conditions associated with SCI can now be prevented or managed more efficiently, for example, spasticity, thromboembolic disease, male sexual dysfunction and infertility, heterotopic ossifications, pressure ulcers, renal failure and respiratory insufficiency. More people with SCI are discharged to their homes[4] and live in the community than ever before and it may be argued, but not proven, that their quality of life has improved over the years with better health, better equipment, more accessible

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urban environment and public recognition of their personal rights.

In contrast to the advances in the care of SCI, decades of intense efforts by basic research scientists have unfortunately achieved little clinically to reverse the neurological loss associated with SCI by protection or regeneration of axons within the injured spinal cord.[5] The neurological outcome of SCI is still first and foremost determined by the extent of the damage that is caused at the moment of injury. No treatment offered today can verifiably change that outcome. Consequently, persons with SCI still must contend with the multiple neurological sequelae of SCI, that is, paralysis, sensory loss, autonomic dysfunction, loss of bladder and bowel control, and so on.

Although better medical care of persons with SCI has helped to progressively improve their health and life expectancy over the last six decades, gains in mobility and self-care skills have remained relatively stagnant because further improvements in these areas are dependent on advancements in basic science that may lead to reversal of the neurological loss. Prognosis for ambulation and independence in the activities of daily living (ADL) continues to be primarily predicted by the neurological level and the neurological completeness of the SCI. Only some compensatory rehabilitation interventions have helped to further increase function, for example, by providing state of the art wheelchairs and other assistive technology, such as communication devices, by emphasizing education and training for career opportunities, by facilitating emotional adjustment by psychological support, by generating an enabling community,[6] and so on.

It is apparent that some of the most significant scientific accomplishments of our civilization during recent decades have been in the field of microelectronics. These have had global impact and revolutionized human communication and access to information. Medicine has benefited enormously from this technological development as a vast array of new medical devices have entered the market after being shown scientifically to be of clinical value, both for diagnosis and treatment of human disease. It may be further argued that creative use of such technology in medicine may result in quicker development of new effective compensatory treatments to improve functions after SCI than the search for a 'cure' through basic regeneration research involving such experimental interventions as grafting and transplantation of Schwann cells, olfactory ensheathing cells, cloned undifferentiated cells or varying types of stem cells. Despite the remarkable knowledge that has been gained in molecular biology during recent years by animal experiments, such as the identification of factors which may inhibit or enhance axonal regeneration, for example trophic factors, guidance molecules and growth inhibitors (Nogo), the profound complexity of human SCI is still only partially understood. Achieving a 'biological cure' for SCI will still require understanding of vast and yet to be discovered scientific knowledge and overcoming enormous scientific obstacles. Although basic regeneration research in this field must be supported as a long-term investment, funding of technological projects to improve function of persons with SCI may prove to be a wiser investment for short-term gains.

The spectacular scientific progress made in electronics and microprocessor technology during recent decades has been utilized by biomedical engineers and clinicians to the benefit of patients suffering from a variety of conditions and disabilities, including SCI. Building on this new technology and on the old knowledge that muscle contraction can be activated by electricity, rehabilitation engineers have designed devices and systems that can apply electrical currents to neural tissues in a synchronized fashion for the purpose of restoring a degree of control over abnormal or absent body functions, a technique referred to as functional electrical stimulation (FES).

Although FES in a pure sense refers to the achievement of certain functional motor activities, for example, standing, transfers, stepping, ambulation, cycling, hand grasp and release, arm reaching, breathing, coughing, bladder and bowel evacuation, penile erection and ejaculation, it is often associated with the considerable therapeutic benefits of physical exercise. Therapeutically, FES has been used to increase muscle bulk, improve cardiovascular performance, prevent and treat pressure ulcers, osteoporosis and joint contractures, control spasticity, and improve general well-being. As a means to maintain the person with SCI in optimal and physical and psychological condition, regular physical therapy, preferably by FES, has been recommended by Kakulas,[5] who notes that regular sensory stimulation through the skin has the effect of keeping retained neurological functions and returning reflexes closer to the normal physiological state. It has been further speculated that the normal neural circuitry within the spinal cord necessary for gait and other motor functions needs continuous maintenance by FES and/or body weight supported treadmill training (BWSTT) ambulation.[7] Others have suggested that such patterned neural activity may be important for both development and recovery of neurological functions.[8] Furthermore, there is substantial scientific evidence that shows that physical exercise not only stimulates production of endorphins, but contributes to the upregulation of brain-derived neurotrophic factor (BDNF), which may promote synaptic and functional plasticity within the brain and spinal cord.[9] In general, it appears that active exercise for the paralyzed body parts is of considerable clinical value for persons with SCI and may be essential for maintenance of neural circuitry should a 'cure' for SCI be found.

Anatomical and physiological principles of FES

To generate muscle contraction by electrical stimulation, the stimulus is generally applied to a peripheral nerve but not to the muscle itself. The electrical stimulus may be applied anywhere along the length of the nerve from its origin to its motor point where it connects with the muscle. Using current techniques, the electrical charge needed to activate a muscle contraction by direct muscle fiber stimulation is too great to be safely applied multiple times. Compared to nerve membranes, the different qualities of muscle membranes are

such that it would require more than 100 times stronger stimulus applied directly to the muscle to generate an action potential than by stimulating the nerve.[10,11] Thus, preservation of the entire lower motor neuron (LMN), including the neuromuscular junction, is essential for all forms of FES, and muscles paralyzed by LMN damage cannot be utilized for FES by using currently available technology.

The strength of the electrical stimulus in terms of amplitude and duration determines the number of nerve fibers activated and the force of the muscle contraction. Large nerve fibers, for example fibers from α-motor neurons, are more easily stimulated than small diameter fibers and because large fibers generally provide innervation for large motor units, these are activated with less current than small motor units. Clearly, sensory fibers within the stimulated peripheral nerve are activated as well as motor fibers, which may be painful, if sensation is preserved. In addition to amplitude and duration of the electrical stimulus, the pulse frequency and waveform are also important. The pulse frequency needs to be high enough to generate a smooth muscle contraction. The stimulus itself may be either monophasic or biphasic, but usually balanced biphasic stimuli are used clinically, as they provide better control over muscle contraction force and are less prone to cause tissue damage.[12,13]

Muscle fibers are primarily of two different types, that is, type I (red, slow, aerobic) and type II (white, fast, anaerobic), and these are histologically and physiologically different. Inactivity is known to lead to transformation of type I muscle fibers into type II, but this change is reversible with appropriate exercise.[14–17] In the paralyzed limbs of persons with SCI, proportionally more muscle fibers are of type II than type I, but the fibers are also atrophied, leading to a weak and fatigable muscle upon stimulation. An exercise regimen of electrical stimulation can increase contraction time and resistance to fatigue,[14] probably as more muscle fibers become type I.

Components of FES systems

Most FES systems are basically quite similar in design and purpose, but the electrical stimulation may be delivered either by surface (transcutaneous), percutaneous or implanted leads and electrodes. The main components of FES systems (Figure 1) include a portable power source (rechargeable battery), command microprocessor/control unit, stimulator, lead wires, electrodes and sensors.[18] Surface FES systems have electrodes that are placed on the skin over the desired nerves or their motor points and these are connected by lead wires to the stimulator, which is carried by the user. Surface FES systems can be safely used by clinicians and are relatively inexpensive, but accurate placement of the electrodes may be difficult and time consuming. It may not be possible to generate isolated contractions of specific muscles and deep muscles may not be activated at all. Additionally, surface stimulation may be painful and the systems visible appearance may be cosmetically unacceptable. Although surface FES system's are adequate for

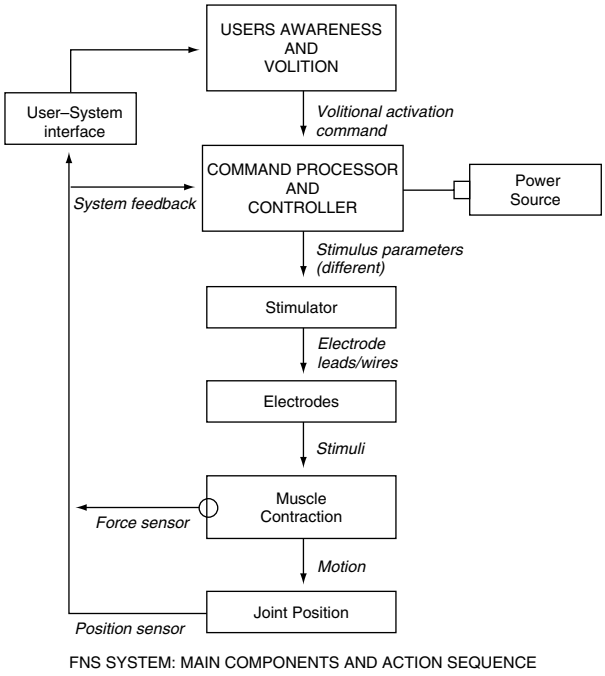

Figure 1 Schematic drawing of a functional electrical stimulation (FES) systems main components and sequence of action (reprinted with permission from Downey and Darling's Physiological Basis of Rehabilitation Medicine, Butterworth Heinemann 2001).

therapeutic or short-term use, implantable systems seem more desirable for long-term use.

Intramuscular electrodes with percutaneous leads have mainly been used during the development of implantable FES systems. To date, they are not part of any FES systems approved for clinical use, but they are undergoing clinical trials for shorter-term muscle conditioning paradigms, such as for relief of pain in shoulder subluxation. They may be inserted through the skin with a large gauge hypodermic needle and placed at the motor point of the desired muscle. When the needle is withdrawn, the electrode remains with the lead wire exiting through the skin and connecting with an external stimulator. In general, percutaneous lead wires appear safe, but with prolonged use, utmost caution is necessary to prevent infection and granuloma formation.[19]

Implanted FES systems are ideal for long-term use. Here, the electrodes, lead wires and stimulator are implanted, but the control unit and the rechargeable battery power source are external. The stimulator receives commands and power through a radiofrequency telemetry link (antenna) from the control unit and batteries respectively, but these are usually externally placed. Unfortunately, the power demands of multichannel FES systems are too great to permit the use of implantable batteries using current technology. Voluntary activation of the system is achieved via external transducers or switches connected to the control unit. The implanted electrodes are surgically placed adjacent to a nerve (epineural), around a nerve via helix or a cuff, or at the motor point on the muscle surface (epimysial) or within the muscle itself (intramuscular). Nerve-based electrodes provide good muscle

specificity and allow stimulation of specific muscles and excellent recruitment with relatively low electrical currents. Care must be taken during the surgical procedure and during long-term stimulation at relatively high frequencies to avoid damage to the nerve. Fortunately, guidelines for safe stimulation have been developed and these electrodes have been used successfully in many applications, such as control of bladder, phrenic nerve for breathing, peripheral nerve stimulation for pain control, and cranial nerve stimulation for epilepsy suppression. Epimysial electrodes generate minimal damage and have proven to be durable for upper and lower limb applications,[20,21] but for activation of deep and very small muscles, intramuscular electrodes are preferable.

Normal motor activity depends not only on synchronized muscle contractions but also on a highly sophisticated sensory feedback processed through innumerable sensory end organs, sensory nerves, the spinal cord and the brain. Unfortunately, modern medical technology does not even come close to providing such sensory information, which is a major shortcoming of multichannel FES systems. Relatively primitive sensory feedback signals from the limbs can be obtained from externally placed goniometers and potentiometers placed at various joints. These can measure joint positions and motion, permitting the systems microprocessor to calculate the velocity and acceleration of movement and consequently adjust and control the stimulator.[22]

The user and the control unit operate the FES system in an interactive fashion. The control unit, which is located external to the body in all currently used FES systems, contains the system's microprocessor (computer, intelligence) and usually the battery. It has three main functions:[13] (a) supplies power from its batteries to the entire system; (b) extracts information from the user and the sensors; and (c) transforms the received information into commands that are transmitted by radiofrequency signals through an externally located transmitting coil to the implanted stimulator. The user is able to control the entire system by varieties of sources, such as a joystick or switches that may use breath force, myoelectric signals, and voice recognition or motion sensors. Depending on the feedback and automatic control provided by the system, the control can be classified either as open loop or closed loop. In an open loop control, preprogrammed patterns of electrical stimulation are individually created for a specific function without automatic correction for changes in muscle force or joint motion. In a closed loop control, the control unit receives information on muscle force and joint motion from the sensors and automatically modifies the electrical stimulation.[23]

Several criteria for effective application of FES have been identified as follows:[13] (a) the strength of the FES-induced muscle contraction must be forceful, controllable and repeatable; (b) the electrical stimulus must not be painful; (c) the LMN must be intact and the neural structures must not be damaged by the FES; and (d) the method of FES delivery must be acceptable to the user. These criteria must be considered when the various methods of applying electrical stimulation are selected for functional purposes.

FES systems for upper limbs

Paralysis of hands and arms in persons with tetraplegia reduces their dexterity, ADL skills, self-sufficiency, and vocational potential. Restoration of tetraplegic hand and arm function has been attempted by various means, for example, therapeutic exercises, orthoses, assistive devices, surgical reconstruction and FES systems, or by various combinations of these. Application of upper limb FES systems is often limited by the extent of LMN destruction within the injured cervical spinal cord. However, many persons with C5 and C6 level tetraplegia have preserved LMN for C7 and C8 neurological segments and can benefit by both surface and implantable FES systems, which may restore a degree of hand grasp, hold and release. Additionally, 12 channel FES systems are currently under development for persons with C4 or higher level tetraplegia who have the C5 and C6 LMN preserved.[24] Such systems are designed to provide shoulder stability and to control elbow flexion and extension to position the hand and the entire arm in space, in addition to providing grasp, hold and release.

Currently, several upper limb FES systems are in clinical use or under development. Candidates for such systems must have intact LMN and minimal spasticity of the muscles to be activated, no significant joint contractures, high degree of motivation, and strong family support. The available systems variously use surface, percutaneous or implanted electrodes. The systems are able to provide palmar prehension to grasp, hold and release relatively large and heavy objects, for example, cans and bottles and lateral prehension for smaller and thinner objects, such as keys, papers and floppy disks.

Surface FES systems for upper limbs

Surface FES systems can be applied during the early rehabilitation of persons with SCI. Such system was first described by Long during the 1960s.[25] More recently, researchers at the University of Alberta developed the Bionic Glove which has not become commercially available, but was used for persons with C6 tetraplegia.[11] This system used a glove with a forearm sleeve worn over surface electrodes that were placed on the skin over the finger flexors and extensors. The electrical stimulation was controlled by voluntary wrist extension for grasping and flexion for release. The clinical benefits of this system were found to be insufficient owing to difficulties with donning, doffing and achieving selective muscle stimulation and sufficient wrist control.[11]

The NESS H200 (formerly Handmaster) system (Figure 2) is currently the only commercially available upper limb surface FES system. It was developed in Israel and consists of a specially designed adjustable wrist hand orthosis with five built-in surface electrodes for finger and thumb extensors and flexors which are capable of generating lateral and palmar grasp and release on stimulation.[11,26,27] A flexible cable connects the orthosis to a portable external control unit with preprogrammed opening/closing stimulation patterns that the user can activate with push button controls. Non-invasive and relatively easy to apply, it

Figure 2 NESS H200 surface FES system for upper limbs (courtesy of Bioness Inc., Santa Clarita, CA, USA).

has been found to enhance the performance of specific upper limb tasks for persons with C5 or C6 tetraplegia[26] and may help to reduce impairments and complications associated with central nervous system (CNS) injuries (www.bionessinc.com).

Percutaneous FES systems for upper limbs

While they were in development, percutaneous electrodes were used for systems that now are fully implantable. One upper limb FES system with percutaneous electrodes, the FESMate was developed and became commercially available in Japan. It consists of a portable 30-channel stimulator/control unit connected to percutaneous intramuscular electrodes that are activated by a push button switch. A later version, that is, NEC FESMate, has a fully implantable 16-channel stimulator and electrodes.[28] These systems have been shown to provide effective palmar and lateral grasp and with its percutaneous electrodes few infections have been reported.

Implantable FES systems for upper limbs

The surgically implantable 'Freehand' FES system (Figure 3) was developed in Cleveland, Ohio[29] and in 1997 it was approved for clinical use by the USA Food and Drug Administration (FDA). It was commercially available until 2001 when the manufacturer withdrew from the SCI market.[11] The Freehand system consists of an eight-channel stimulator/receiver implanted in the anterior chest wall and connected to eight epimysial or intramuscular electrodes for the finger flexors and extensors which on stimulation generate palmar and lateral grasp. The external components include a radiofrequency transmitting coil, which is taped to the skin on the chest over the implant, a programmable external control unit and a sensor (transducer) for detecting contralateral shoulder motions. The movement of the contralateral shoulder proportionally controls the degree of hand opening and closing.[11,27] The Freehand system has been implanted in more than 250 individuals with C5 and C6 tetraplegia, 51 of whom participated in a multicenter clinical trial where function was measured before implantation and after implantation and rehabilitation, as well as with and without the Freehand system.[30] Virtually all of the participants were found to have greater pinch force, better grasp and release, greater ADL independence, and they expressed high satisfaction with the Freehand system, which was noted to be safe and associated with very few medical complications during a total of 128 cumulative implant years. Other investigators have reported similar beneficial clinical results.[31,32] It is regrettable that the manufacturer of the Freehand system chose to withdraw from the relatively small SCI market for business reasons.

The Freehand stimulator is surgically implanted in a subcutaneous pocket over the fascia of the pectoralis muscle on the chest wall on the ipsilateral side, after an incision has been made in a sensory intact skin.[33,34] More recently, minimally invasive surgical techniques have been used for its implantation.[35]

Surgical reconstruction of the tetraplegic hand has long been known to improve function for those who meet the clinical criteria.[36] Hand reconstruction has also been used in combination with FES, especially when electrical stimulation of the usual muscles cannot generate sufficient grasp and release and no adjacent voluntary muscles can be transferred.[37] For such clinical conditions, spastic hand muscles paralyzed by UMN lesion and located in proximity to flaccid paralyzed muscles or their tendons can be transferred to flaccid muscles, similar to traditional transfers of tendons from voluntary contracting muscles. Furthermore, thumb and finger joints can be selectively fused to substitute for paralyzed muscles and thus to improve hand function. The transferred spastic muscles are subsequently electrically stimulated for functional purposes using the Freehand system.

Elbow extension is a desirable but absent function for individuals with SCI and neurological level at C6 or higher. If the C7 motor neurons are present, electrical stimulation of the triceps muscle motor points as an addition to the Freehand system has been shown to increase the users ability to reach and move objects, but such FES system was not brought to the market.[38]

A second-generation implanted FES upper limb system, (Figure 4), has been developed and is being clinically tested,[11,27,39] but it has not yet been marketed. Here, greater number of stimulation channels/electrodes allow activation of greater number of muscles (12), which results in better upper limb function, for example, better grasp and release, and additionally it can provide forearm pronation and reaching by elbow extension. Myoelectric signals from implanted wrist-joint sensors and electromyography of voluntary muscles, usually wrist extensors, are transmitted to the control unit and stimulator which allows the user to

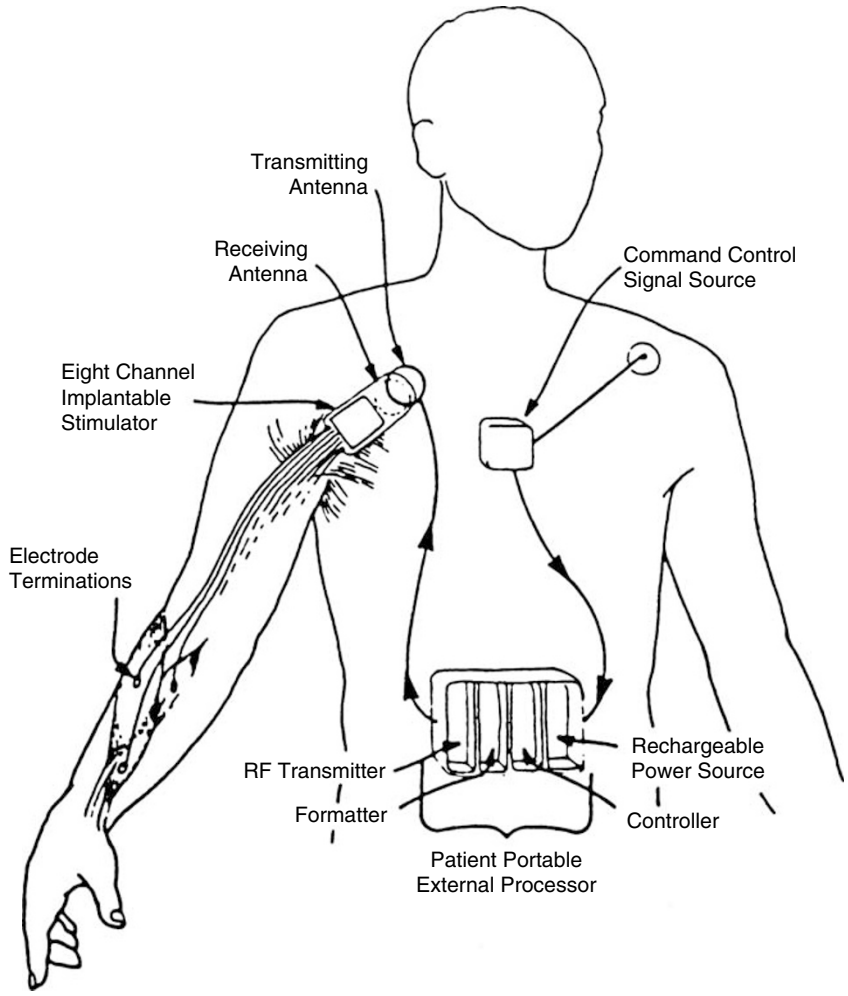

Figure 3 First-generation implantable FES system for upper limbs (reprinted with permission from Keith MW, Peckham PH, Thrope GB *et al*. (1988). Functional neuromuscular stimulation, Neuroprosthesis for the tetraplegic hand. *Clin Orthopaedics* **233**: 25–33).

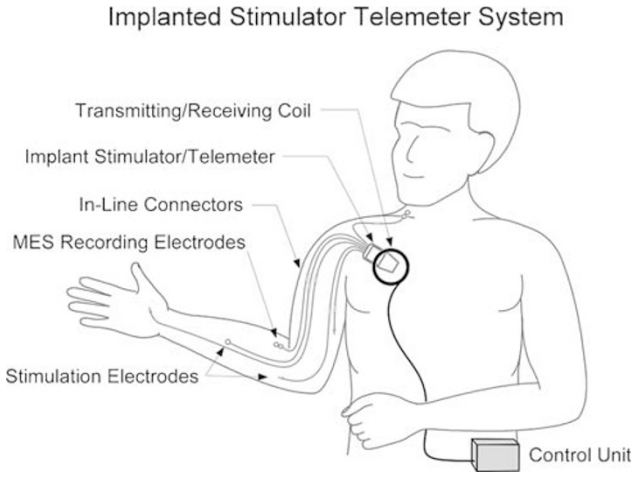

Figure 4 Second-generation implantable FES system for upper limbs (courtesy of PH Peckham, Cleveland FES Center, Case Western University).

control the system by use of ipsilateral muscles, usually wrist extension for grasp and wrist flexion for release. Other muscles under voluntary command can also be used, for example, shoulder and neck muscles to control the system. This advanced system eliminates the need for contralateral external shoulder position sensor and permits the system to be implemented bilaterally. The system can be programmed in an individualized manner, using up to 12 channels for stimulation and different ipsilateral control mechanisms, for example, implanted wrist joint sensor or myoelectric signals. The system has been implanted in 12 persons with tetraplegia[27] and preliminary studies indicate that effective grasp and release can be achieved and function improved with high level of user satisfaction.

Future directions. The promising aspects of the implanted system, which is now being tested clinically, addresses many shortcomings of previous upper limb FES systems, that is, it has ipsilateral muscle control, more implanted components, greater number of muscles to be stimulated, capable of

providing elbow extension, streamlined programming capabilities and permits implantation in both upper limbs. The batteries and control unit are still external to the body, but may be implantable before long using a radiofrequency link to power and to control the system. Minimally invasive surgical techniques may permit earlier implantation with less trauma and earlier restoration of hand function. Further miniaturizing of the system's components and total implantation of the entire system will undoubtedly increase its acceptance by users who have C5–6 tetraplegia. Development of implanted upper limb FES systems for persons with high tetraplegia, that is, C4 or higher, may also be possible with further advances in technology and surgical techniques,[40] that is, by nerve, muscle and/or tendon transfers.[41] A clinical trial is soon to begin with a device known as Micropulse II (NDI Medical, Cleveland, OH, USA), which has many of the features described above but is also internally powered and wirelessly controlled allowing elimination of the external coil and control unit.

FES systems for lower limbs

During the early phases of rehabilitation, most persons with SCI and their families hope for restoration of lower limb neurological function sufficient at least to allow standing and walking. Despite use of lower limb orthoses of various design, energy efficient ambulation is still not possible for persons with tetraplegia and thoracic paraplegia. Ever since 1960, when Kantrowitz reported that persons with paraplegia could stand during electrical stimulation of both quadriceps muscles simultaneously,[42] have investigators in numerous laboratories worldwide attempted to generate FES systems to allow persons with SCI to stand and walk, but they have had limited success. Even with the most advanced implanted multichannel closed loop control FES systems and the use of most modern orthoses, standing, transferring and short distance stepping supported by a walker is the most significant function that currently can be obtained by this means.

There are numerous physiological and bioengineering reasons for the inability to create FES systems for functional walking, that is, high-energy expenditure, slow speed of gait, absent lower limb proprioception, poor balance, insufficient exercise response in persons with high thoracic or cervical level SCI, lack of large and stable muscle forces for stimulation, inadequate coordination of muscle activation for efficient energy consumption, shortcomings in system design, for example, reliance on visual feedback, user control, heavy batteries, bulky and unreliable hardware, and so on.[13] Although the functional value of standing, transferring and stepping by means of FES is clinically significant, it is not anticipated that FES systems will replace the wheelchair as the main mobility aid for persons with SCI.[11,13] Many surface FES systems have been tested by various investigators and one such system, Parastep (Figure 5), is commercially available in the United States and many other countries. Hybrid systems, combining FES with a reciprocating gait orthosis (RGO), have been tested extensively but have not reached the commercial market. Currently, an implanted FES system (Figure 6) for standing and transfers is being clinically tested.[43–45]

Figure 5 Parastep surface FES system for lower limbs (courtesy of Therapeutic Alliances Inc., Fairborn, OH, USA).

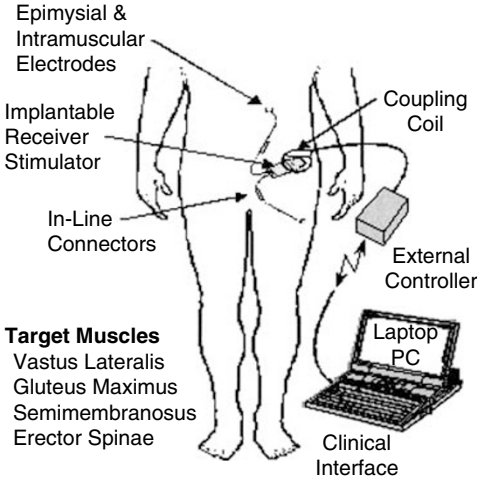

Figure 6 Schematic drawing of the 'CWRU Standing System', an implantable FES system for lower limbs (courtesy of R Triolo, Cleveland FES Center, Case Western University).

During the development of lower limb FES systems, it has been observed that regular electrical stimulation of paralyzed lower limb muscles induced exercise-related physiological changes, which were felt to have some therapeutic benefits. On the basis of this observation, FES cycle ergometers have been designed and extensively tested and prescribed for persons with SCI based on established clinical benefits.

Regardless of the type of FES system considered for standing, transfers and stepping, it is important to recognize that (a) the best candidates are persons with T4–T12 paraplegia who have intact lumbo-sacral LMN and good upper body strength; (b) a walker is needed for standing stability and safety; (c) most systems require the user to wear ankle foot orthoses (AFO); and (d) the speed of walking is slow and the energy expenditure is high.

Surface FES systems for lower limbs

As Kantrowitz demonstrated in 1960, persons with paraplegia can stand by simultaneous electrical stimulation of the quadriceps muscles bilaterally.[42] Later, Kralj *et al*.[46] and Bajd *et al*.[47] in Slovenia, demonstrated that stimulation of the peroneal nerve generates reflex withdrawal with flexion of the hip, knee and ankle joints, a motion that can simulate the swing phase of gait. Stepping occurs when the quadriceps muscle on the stance side is stimulated for knee extension, whereas simultaneous peroneal nerve stimulation causes flexion withdrawal on the swing side, followed by quadriceps stimulation on the swing side, whereas the reflex is still generating hip flexion. When the withdrawal reflex subsides, both quadriceps muscles are stimulated to create knee extension during the period of double support of the gait cycle.

On the basis of these findings, a lower limb surface FES system was built, tested, FDA approved, and made commercially available in 1994 under the brand name Parastep[48] (Figure 5). This system uses four or six channels for bilateral stimulation of the quadriceps muscles and the peroneal nerves and optionally, when six channels are used, for the gluteus muscles. The microprocessor control unit and battery pack are worn at the waist and the user controls the system with push buttons built into a walker. After meeting certain clinical criteria,[49] more than 750 persons with SCI, mostly those with neurologically complete thoracic level paraplegia, have obtained the Parastep system. One study showed that following 20–30 training sessions, virtually all of the 16 subjects became able to stand and ambulate using the Parastep system with a walker for short distances.[49]

Another follow-up study of 13 subjects showed that users of the Parastep system found it easy to operate and be cosmetically acceptable, but it had relatively limited value for mobility in daily life due to the high-energy expenditure associated with ambulation by this means.[50] However, it was felt to have value as a resource to maintain physical and psychological fitness. No large follow-up studies regarding continued use of the Parastep system have been reported.

Percutaneous and implanted lower limb FES systems for lower limbs

Using the principles described above, development of implanted FES systems began during the 1980s, with the investigators depending on insertion of percutaneous electrodes for stimulation,[51] which enable better activation of deep muscles and more reliable responses than surface electrodes. Activation of as many as 48 different muscles by this means was shown to allow more complex lower limb motions to be performed,[52] although such complex system was never fully developed for extensive clinical use. More recently, several groups of investigators have developed implantable FES systems for standing and ambulation,[53,54] but none of these have undergone sufficient clinical trials. A 12-channel FES system for stimulation of L2–S2 motor roots was designed and tested,[53] but was found to provide inadequate selectivity for muscle activation and consequently further development of this system was abandoned. Based on the success of cochlear implant technology, another group built a 22-channel implantable FES system, which was found to permit standing and limited swing-through gait in two subjects,[54] but its further development has been abandoned.

For long-term use, implanted FES systems are felt to be superior to surface and percutaneous systems with respect to their convenience, cosmesis and reliability.[27] Recognizing the inherit limitations of such FES systems as well as their simple but significant benefits of allowing standing, transferring and stepping, it has been possible to more clearly identify the optimal number of muscles in the lower limbs to be stimulated and subsequently to reduce the number of desired electrodes.

Currently, a first generation implanted lower limb FES system for standing, trunk support and swing to/through gait is being clinically tested at the Cleveland VA Medical Center and Case Western Reserve University, that is, the VA/CWRU Standing System[27,43] (Figure 6). The implanted components consist of an eight-channel receiver/stimulator, epimysial and/or intramuscular electrodes and connecting wires, whereas the external components include the control unit, rechargeable batteries and a clinical programming station.[27] The electrodes are implanted into the quadriceps, gluteus and lumbar erector spinae muscles bilaterally. One subject with an incomplete SCI has received the eight-channel implant, enabling reciprocal gait using a rolling walker for stability. Reciprocal stepping in patients with complete SCI can be achieved with 16 channels of stimulation and by adding implanted electrodes to activate the hip flexors and ankle dorsiflexors.[27,55] Using this system, subjects were able to stand with a walker and optional AFO's for more than 10 min on the average and some were able to release one hand from the walker and perform reaching tasks above the shoulder while standing.[27] Most subjects supported over 90% of their weight in their lower extremities. Performance during reciprocal stepping has not been reported but swing-through gait is possible for variable distances. Stimulation of the lumbar erector spinae and gluteus muscles bilaterally during sitting allows better trunk control and seated posture[56] without the need to lean on the backrest or use hand support to prevent jackknifing.

Hybrid FES systems for lower limbs

Most lower limb FES systems include the optional use of bilateral AFO's, but hybrid FES systems generally refer to the simultaneous use of FES and RGO in an attempt to improve stability during standing and ambulation, as well as to reduce energy cost.[45,57,58] Such hybrid FES systems require

the user to wear the RGO,[59] which is a knee-ankle-foot orthosis connected to a thoracolumbosacral orthosis by hip joints and a cable coupling mechanism, whereas four-channel surface electrical stimulation is delivered to the rectus femoris muscle for hip flexion and to the hamstring muscles for hip extension. Studies have shown that hybrid FES systems moderately decrease energy expenditure compared to ambulation with either FES or RGO alone,[45,57,58] but short stride length and mechanical difficulties with the RGO present significant clinical drawbacks,[27] which have prevented widespread use.

Future directions

The energy cost of paraplegic ambulation at functional speeds with orthoses, FES systems and combinations thereof is such that these devices cannot be used practically for long distance locomotion and therefore are not expected to replace the wheelchair as a mobility device.[60–62] However, lower limb FES systems can provide relatively effortless standing, permit overhead reaching with one arm, allow trained individuals short distance stepping which is useful for transfers and for locomotion within small spaces and additionally they can improve sitting balance and posture. Exact identification of the minimum number of muscles needed for such relatively simple tasks and the development of a small, totally implantable FES system (similar to cardiac pacemakers) capable of generating the desired functions would provide significant benefits for many persons with SCI.

For persons with neurologically incomplete SCI, combined use of FES and BWSTT may prove to be more effective in improving their ambulation skills than other clinical approaches.[63–65] In contrast to ambulation with orthoses, which generate exclusively upper body exercise, ambulation with lower limb FES systems generates active contraction of lower limb muscles which may have significant health benefits as is discussed below.

FES systems for respiratory muscles

A degree of respiratory insufficiency is present in all persons with neurologically complete tetraplegia due to the loss of intercostal muscle innervation, but the diaphragm, which is innervated by the phrenic nerve, permits ventilatory free breathing for most. The phrenic nerve consists of nerve fibers that derive primarily from C3, C4, C5 and even C6 LMN and nerve roots, but most of its nerve supply comes from the C4 neurological segment. Therefore, virtually all persons with neurological level at or below C4 will be able to breathe without the assistance of mechanical ventilation. An injury to the spinal cord above C4 level will result in respiratory failure requiring mechanical ventilatory assistance, often permanently. A severe injury exactly at the C4 cord level may destroy the LMN's for C4 and even for C3 and C5 LMN as well, but a complete transverse lesion at C1 and C2 levels may leave those neurons and hence the phrenic nerves relatively or even completely intact, albeit without supraspinal control. A clinical condition that spares the C3, -4 and -5 LMN's may allow electrical stimulation of the phrenic nerves for ventilator-free breathing, a technique generally referred to as electrophrenic respiration (EPR) or sometimes as phrenic nerve pacing.

Clinical guidelines for choosing candidates for EPR have been described by Carter *et al*.,[66] but the most important criteria are to have proven viability of the phrenic nerve, healthy lungs and airways, good sitting tolerance, strong desire and motivation, family support and professional technical knowledge. Because spontaneous recovery of diaphragmatic function occurs in many persons with high SCI during the first year after injury, it is generally felt to be appropriate to wait at least 4–6 months after the SCI before EPR is considered.

Evaluation of diaphragmatic function usually begins by establishing the absence of voluntary diaphragmatic motion during fluoroscopic examination of the chest. This is followed by electrical stimulation of the cervical portion of the phrenic nerve, whereas simultaneously monitoring diaphragmatic responses by electromyography using surface recording electrodes located between the seventh and ninth intercostal spaces[66] during stimulation. The latency and conduction time of the phrenic nerve should be recorded to assess its integrity and a fluoroscopic examination of the chest should be done to measure the diaphragmatic excursions, which should be 4.5–6 cm bilaterally.[66]

EPR was first developed for central hypoventilation syndrome, often referred to as Ondine's Curse, but through the pioneering efforts of Glenn *et al*. it has been used since the 1970s for persons with SCI and neurological levels of C3 or higher. Currently, at least three EPR systems are commercially available but these are fundamentally similar in design, that is, the Avery Breathing Pacemaker System by Avery Laboratories (Commack, New York, NY, USA), which is FDA approved and currently has the widest use (Figure 7), the Atrostim Phrenic Nerve Stimulator by Atrotech (Tampere, Finland), which is FDA approved for investigational use only, but widely available outside the United States, and the MedImplant by MedImplant Biotechnisches Labor (Vienna, Austria), which is available in Europe, but not in the United States. Each of these systems has phrenic nerve stimulating electrodes implanted bilaterally in the cervical or thoracic regions, radiofrequency receiver/stimulator implanted under the skin on the anterior chest wall and lead wires implanted to connect the two main components. The stimulator receives radiofrequency command signals from an externally located control unit and power from a rechargeable battery, both transmitted via an antenna, which is taped to the skin directly over the implanted receiver/stimulator. Stimulation of the phrenic nerve results in contraction of the diaphragmatic muscle with descent of the diaphragm that creates a negative intrathoracic pressure and inhalation of air. When the stimulation stops, the diaphragm relaxes and ascends, resulting in exhalation. The amplitude and frequency of the stimulus is manually adjustable, but ordinarily 8–14 stimuli per minute are required for adequate ventilation.

The main differences between the three EPR systems lie in the electrodes. The Avery system uses monopolar or bipolar nerve cuff electrodes, but the Atrostim system uses a four-pole sequential stimulation, that is, each electrode makes four

evenly spaced contacts with the phrenic nerve. These contacts are stimulated sequentially, apparently activating different parts of the nerve (axons) and diaphragmatic muscle, which may delay diaphragmatic muscle fatigue.[67,68] The MedImplant system uses a so-called 'Carousel' stimulation where four electrodes are sutured to the epineurium of each phrenic nerve and connected to a single eight-channel receiver/stimulator.

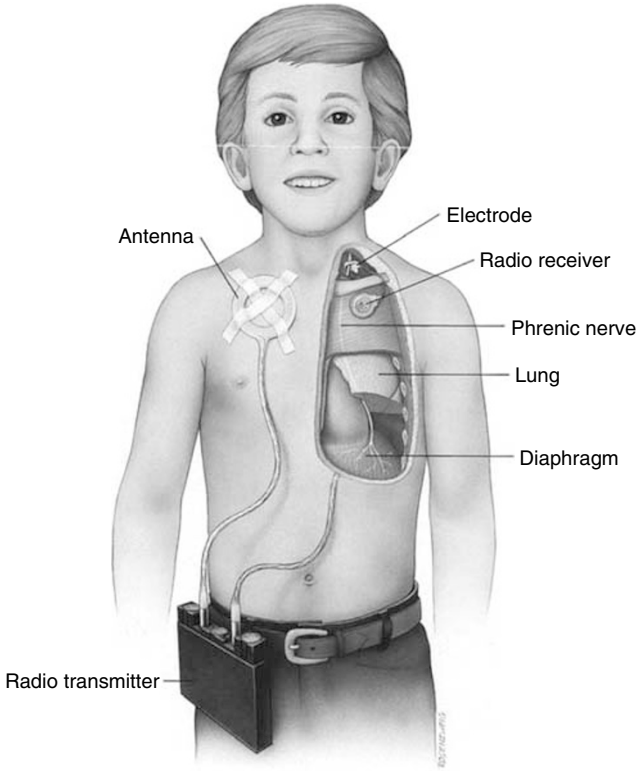

Figure 7 Avery Breathing Pacemaker System, an FES system for respiratory muscles by phrenic nerve stimulation (courtesy of Avery Biomedical Devices, Commack, NY, USA).

One of the four electrodes is used to stimulate each nerve sequentially, also aiming to reduce muscle fatigue.[11,68]

Surgical implantation of EPR systems may be done by a cervical or preferably by thoracic approaches.[68,69] Although the cervical approach is less invasive as it avoids the need for thoracotomy, an electrical stimulus of the phrenic nerve in the neck may result in submaximal response or cause pain by stimulation of other nerves in the neck. The phrenic nerve in the thorax is usually accessed by incisions through the second or third intercostal spaces and the electrodes are secured behind or over the nerve. The receiver/stimulator is implanted subcutaneously through a second incision, which is usually made in the lower anterolateral chest wall and connected to the electrodes by wires placed subcutaneously. In recent years, minimally invasive laparoscopic techniques have permitted implantation of intramuscular diaphragm electrodes near the diaphragm's motor points[70–72] (Figure 8), a technique which reduces the length of surgery time and minimizes the trauma to the person.

Postoperatively, the diaphragm is gradually reconditioned to reverse disuse atrophy and to regain strength and endurance. To allow for adequate healing, stimulation is usually not started until 2 weeks postoperatively by using supramaximum stimulus amplitude and the lowest frequency capable of generating diaphragmatic response.[73] Stimulation is initially done daily for 10–15 min every hour and gradually increased, but it may take 2–3 months before muscle reconditioning is considered complete. An early goal is to allow ventilator-free breathing by EPR during the waking hours only, followed by EPR during sleep as well. Respiratory rate is usually 8–12 breaths per minute and tidal volume 500–750 cm^3. For users of the Avery and Atrostim systems, the tracheostomy is generally kept open, but reportedly most users of the MedImplant system have had the tracheostomy closed without ill effect.[74] The open tracheostomy may be capped, especially during waking hours, but by leaving it open, suctioning and removal of secretions is made easier and mechanical ventilation may be

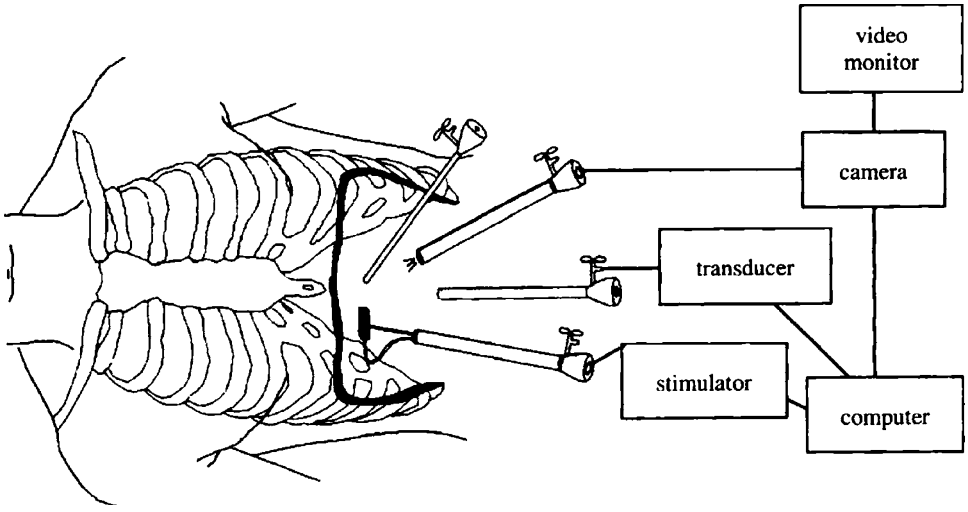

Figure 8 Implanted intramuscular electrodes near the diaphragms motor points (reprinted with permission from DiMarco AF, Onders RP *et al.* (2002). Phrenic nerve pacing in tetraplegic patient by intramuscular diaphragm electrodes. *Am J Crit Care Med* **166**: 1604–1606.

restarted when medically necessary. Throughout the conditioning phase and whenever the user experiences difficulty breathing as well as periodically during follow-up, the EPR function should be monitored by assessing tidal volumes and blood gasses, as well as diaphragmatic excursions.[75,76]

EPR is generally felt to be safe and effective and its users describe multiple advantages over mechanical ventilation, for example, greater comfort and sense of well-being, improved breathing and speech and better cosmesis.[77,78] In general, the incidence of complications and EPR system failures is low but all users should have immediate access to mechanical ventilation or other means of ventilatory support when respiratory emergencies arise. No recent longitudinal follow-up studies are available to describe the successes and failures of EPR, but anecdotal reports describe damage to the phrenic nerve due to direct mechanical trauma, compromise of nerve blood supply and fibrosis around the electrode.[73,77,79,80] The incidence of nerve injury may be reduced by use of monopolar electrodes or perhaps by sequential stimulation provided by use of the Atrotech and MedImplants systems. Failure of EPR systems may be related to dysfunction of batteries, antennas, receiver/stimulator, wires or electrodes, all of which need to be evaluated systematically when failures occur. As with all implanted electronic systems, magnetic resonance imaging (MRI), shock wave lithotripsy and various types of diathermy, which generate strong radiofrequency fields, are contraindicated. Respiratory complications do not appear to be any more common than among persons requiring mechanical ventilation, provided that patients are properly selected, stimulation parameters are carefully determined and continuous monitoring is available. Upper airway obstruction, usually by accumulation of airway secretions, requires prompt suctioning, optimally via open tracheostomy. Furthermore, tendency for negative inspiratory pressure and upper airway collapse during sleep is alleviated by maintaining an open tracheostomy, although during waking hours, capping of the tracheostomy is appropriate and safe.

Future directions

Compared to mechanical ventilation, EPR offers an attractive alternative that may increase the physical and emotional comfort, mobility, communication, cosmesis and social integration of persons with tetraplegia and respiratory insufficiency. Unfortunately, relatively few individuals with tetraplegia use this method of ventilation, as mechanical ventilation continues to be the standard of care. A possible underutilization of EPR may be related to the high cost of surgical implantation and lengthy reconditioning phase, as well as medical factors such as damage of the phrenic nerve. Potential candidates for EPR may be ignorant of its benefits or reluctant to have surgical implantation done many months or even years after completing their inpatient rehabilitation. Additionally, EPR systems have certain shortcomings. As noted above, stimulation of the phrenic nerve causes a contraction of the diaphragmatic muscle, resulting in inhalation only, but exhalation is passive. Therefore, EPR does not produce an effective cough which would be generated by a combined and synchronized contraction of the abdominal and intercostal muscles, a function that none of the available EPR system provides. Furthermore, contraction of the diaphragm by EPR is independent of upper airway muscle activation, which places the user at a risk of upper airway obstruction during sleep. Owing to these two factors, EPR users need to have an open tracheostomy to secure safe breathing during sleep and to permit suction of secretions.

It may be argued that more persons with tetraplegia who are ventilatory dependent could become users of EPR, if damaged phrenic nerves could be repaired by nerve grafting techniques,[81] if cost of implantation could be reduced by placing electrodes less invasively and less costly through laparoscopic surgery,[72] and if implantations of electrodes were performed laparoscopically earlier after SCI than is currently done. Early implantation of electrodes and regular stimulation may reduce the need for lengthy reconditioning of the diaphragmatic muscle which might facilitate weaning off the ventilator, if phrenic nerve function returns, a development which would permit removal of the electrodes and the entire EPR system.

In recent years, it has been shown that accurate mapping of the phrenic nerve motor points permits successful laparoscopic implantation of intramuscular electrodes within the costal portion of each hemi-diaphragm.[51,73,71,72] Such procedure involves placement of four laparoscopic ports to the abdominal cavity for creation of a pneumoperitoeum, visualization of the diaphragm, diaphragmatic mapping by electrical stimulation and implantation of two electrodes at the motor points in each hemi-diaphragm.[73] The electrode wires are tunneled subcutaneously to the chest wall where they exit and connect to an external stimulator. Such system is felt to be low risk, cost-effective and implantable during and outpatient visit.[71] Early implantation, even within weeks of acute SCI, of all system components is ultimately envisioned.[71]

DiMarco *et al*.[73] have recently described in detail shortcomings of currently used EPR systems and outlined needs for their further development. In most cases, viability of only one phrenic nerve is not sufficient to allow breathing exclusively by EPR only. A development of an intercostal muscle FES system, which could be used simultaneously with a unilateral EPR, may generate effective ventilation and eliminate the need for mechanical ventilation. There also is need to develop an FES system for abdominal muscles that upon stimulation would generate a more forceful active expiration and cough.[82–85] There is need to synchronize the upper airway muscle activation with diaphragmatic activation to reduce the risk of upper airway obstruction during sleep. This might reduce the need for maintaining an open tracheostomy. There is need to develop a totally implantable EPR system, similar to cardiac pacemakers, with elimination of all the external hardware, for example, stimulator/receiver, antenna and battery power source. This would make EPR systems more attractive to potential users. Muscle fatigue continues to be prevalent among some users of EPR. It is possible that sequential stimulation, such as is currently provided by Atrostim and MedImplant Systems will reduce development of such fatigue.

FES systems for bladder, bowel and sexual function

Contraction of the bladder by electrical stimulation of the pelvic nerves was reported as early as the mid-nineteenth century.[86] This observation led to attempts to improve micturition in persons with SCI by stimulation of the conus medullaris, sacral nerve roots, pelvic nerves or even the bladder itself, usually with unreliable results. Anatomical studies revealed that the sacral nerve roots originating in the conus medullaris provide somatic motor axons to the external urethral and anal sphincters through the prudendal nerves and also provide parasympathetic pre-ganglionic efferent axons to the smooth muscles of the bladder, rectum, sphincters and erectile tissue through the pelvic splanchnic nerves. Sensory fibers from these organs also enter the conus through the sacral nerve roots. During the 1970s, Brindley reported the implantation of the first sacral anterior root stimulator (SARS) for bladder control, which were initially done in animals, but subsequently also in humans.[87,88] Refinement of this approach led to the development of the Finetech–Brindley bladder system (marketed as 'Vocare' in the USA) (Figure 9) which has been implanted in more than 2000 individuals worldwide and has been FDA approved in the USA. Successful application of this system has been shown to produce bladder emptying and continence.[89]

Electrical stimulation of the sacral anterior nerve roots not only results in contraction of the detrusor muscle of the bladder, but also of the external urethral sphincter, which may not appear to be ideal for effective voiding. However, Brindley[90] showed that intermittent bursts of stimulation for a few seconds interspersed with intervals of no stimulation can generate sustained detrusor contraction while permitting the sphincter to relax rapidly during periods of no stimulation and thus permit passing of urine. Longer bursts of such stimulation and intervals can produce defecation for some users.[91] In order to secure urinary continence between stimulations, increase bladder capacity, decrease detrusor and sphincter dyssynergia and lower the risk of autonomic dysreflexia, it is usually necessary to interrupt the reflex arc by performing S2–4 posterior rhizotomy,[92] which unfortunately is associated with irreversible loss of reflex erection and ejaculation.[93]

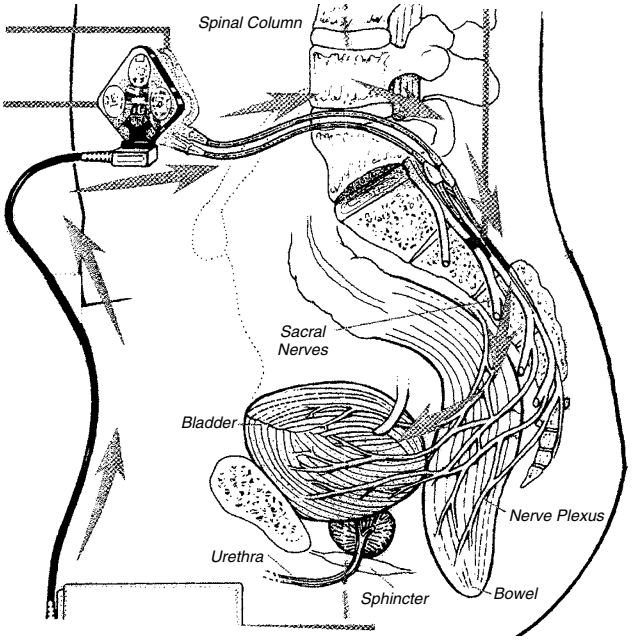

Figure 9 Vocare, implanted FES system for bladder (and bowel) control (courtesy of Neurocontrol Inc.).

The Finetech–Brindley bladder FES system consists of surgically implanted components activated by an external transmitter, which is operated by the user. The electrodes are usually implanted bilaterally and extradurally on the S2, -3 and -4 nerve roots by S1–S3 laminectomy.[93] Intradural placement on the anterior (motor) sacral roots may be preferable for more accurate stimulation but is felt to increase the risk of sacral spinal fluid leak and nerve trauma. The electrodes are connected by lead wires to a receiver/stimulator implanted on the anterior abdominal wall. The implant is powered and controlled by an external control unit with a transmission antenna. Posterior sacral rhizotomy is performed by T11-L2 laminectomy which gives exposure of the conus medullaris and the cauda equina.[93]

Candidates for bladder FES system must have neurologically complete suprasacral SCI and documented problems with other forms of bladder management, for example, more than three urinary tract infections during the preceding year, uncontrollable reflex incontinence.[93] Follow-up studies[89,93] have shown that 80–90% of users can urinate on demand with post-voiding volumes of <50 ml. Bladder capacity generally increases to more than 400 ml and continence between stimulation is achieved in more than 85% of cases. At the same time, urinary tract infections, catheter use, anticholinergic drug use and autonomic dysreflexia were all greatly reduced.[93] The most common postoperative adverse event was stress incontinence.[93] Although implant failures occur, they are rare as mean time between implantation and failure is almost 20 years.[94]

Defecation

Electrical stimulation of the sacral anterior nerve roots and parasympathetic nerves has been shown to increase colorectal motor activity,[95] which increases the frequency of defecation and reduces constipation. By adjustment of the electric stimulus parameters, that is, by lengthening the intervals between burst of stimulation, passage of stool may occur. Users of the bladder FES system have noted significantly less time spent on bowel evacuation and reduced use of suppositories[5]and generally improved bowel function[96,97] as fecal incontinence is not increased.[93]

Erection and ejaculation

Electrical stimulation of the intact sacral anterior nerve roots, especially S2, has been shown to produce penile erection which will last as long as the stimulus is sustained.[98] Effective erection may thus occur with the use of the FES bladder system but given other currently available means of achieving erection after SCI, induction of erection is not felt to be an indication for implantation of such systems.[99]

Ejaculation may be generated by electrical stimulation via electrodes implanted on the presacral (hypogastric) sympathetic plexus,[100] but this method has not been applied

clinically, as semen can usually be obtained more easily by electro-ejaculation using a temporarily inserted rectal probe.[99]

Future directions

The need for posterior sacral rhizotomy resulting in loss of reflex erection has been the greatest clinical drawback of the bladder FES systems. It has been demonstrated that stimulation of afferent nerve fibers within the pudendal nerve or sacral nerve roots[101,102] can result in relaxation of the detrusor muscle, a phenomenon referred to as neuromodulation, that is, the influence of activity in one neural pathway affects the pre-existing activity in another by synaptic interaction.[102] It has been shown that neuromodulation can be used in combination with bladder FES systems. Here, simultaneous stimulation of the sacral posterior and anterior nerve roots can suppress detrusor hyperreflexia and increase bladder capacity.[103] Although there was incomplete bladder emptying in the five subjects in the study, such techniques utilizing natural inhibitory reflexes may ultimately eliminate the need for posterior rhizotomy. It has also been suggested that a fast acting and quickly reversible neural block can be created by electrical techniques that provide unidirectional propagation of electrical signals or by use of high-frequency alternating currents.[13,104]

Therapeutic effects of FES

SCI adversely affects the physiological functions of most organ systems.[18] Most of these changes are directly related to the loss of supraspinal control over voluntary and autonomic functions, but they are compounded by the sedentary lifestyle enforced by the disability and the lack of appropriate exercise programs for persons with SCI. Table 1 shows some of the clinical conditions associated with SCI sedentary lifestyle and lack of physical exercise, conditions which may be partly reversible by FES and other forms of exercise, for example, BWSTT and wheelchair sports.

These conditions will be briefly discussed with respect to their occurrence in persons with SCI and observed therapeutic effects of FES-induced exercise. In general, the effects of physical exercise on these conditions is directly related to the size of the muscle mass involved and the duration of the activity, that is, lower limb exercise is more effective than upper limb exercise, and sustained activity is more effective than brief spurts. Although ambulation by FES would likely have a therapeutic effect, it is not easily achieved or available to most persons with SCI and has not been studied much in this respect. In contrast, FES leg cycle ergometers (FES-LCE) have been FDA approved, commercially available for more than 20 years and their use extensively studied (Figure 10).[17,105–108] It may be speculated that FES used in combination with BWSTT[63] may have similar and perhaps additional therapeutic effect on persons with SCI.

Table 1 SCI clinical conditions associated with sedentary lifestyle and lack of exercise

1	Cardiovascular deconditioning
2	Decreased serum high-density lipoprotein
3	Increased body fat mass
4	Diabetes mellitus
5	Leg edema
6	DVT
7	Decreased muscle bulk, strength and endurance
8	Pressure ulcers
9	Osteoporosis
10	Depression
11	Impaired neural plasticity

Abbreviations: DVT, deep venous thrombosis; SCI, spinal cord injury.

Cardiovascular deconditioning

Cardiovascular fitness expressed as physical work capacity and maximum oxygen consumption (VO_2 max) is reduced in most persons with SCI, but especially in those with complete high cord lesions. There are two main reasons for this reduction. First, there is loss of supraspinal control over the autonomic nervous system that results in inadequate exercise response (sympathetic) and over the numerous striated muscles that cannot be activated voluntarily for exercise. Second, physical inactivity and sedentary lifestyle reduces cardiovascular fitness. Although the loss of supraspinal control cannot be altered, numerous studies have shown that aerobic capacity can be increased, even many years after SCI with FES-LCE training.[106,107,109]

Decreased serum high-density lipoprotein – cholesterol

Lipid profiles are negatively affected immediately following SCI. Although total cholesterol levels may be normal, serum

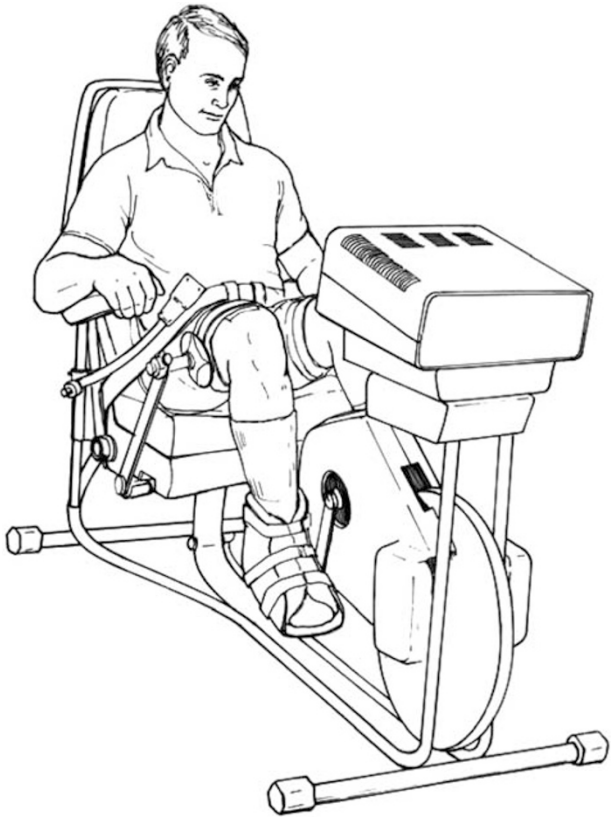

Figure 10 FES leg cycle ergometer for lower limb exercise (reprinted by permission from Downey and Darling's Physiological Basis of Rehabilitation Medicine, Butterworth Heinemann 2001).

high-density lipoprotein cholesterol (HDL-C) is significantly lower in persons with SCI than in the able-bodied population,[110–113] a finding that has been felt to be related to low levels of physical activity. Among persons with SCI, serum HDL-C has been found to be higher in women than in men, and in wheelchair athletes than in persons with SCI who are physically inactive.[110] Serum HDL-C has been noted to rise modestly during the first 2 years after SCI[113] and in general, serum HDL-C levels have been shown to rise in persons with or without SCI with increased physical activity, increased aerobic capacity and by participation in sports activities.[110,111,114] Persons with motor complete SCI tend to have lower HDL-C than those with incomplete SCI.[115] Currently, it is not known if the physical exercise associated with FES-LCE training is sufficient to raise serum HDL-C in persons with SCI but it has been shown that both upper limb exercise training for endurance and strength as well as dietary intervention affects lipid profiles favorably.[116,117]

Increased body fat mass

Being overweight or obese is common among persons with SCI,[118] even more so than in the general population. Even when body mass index, that is, body weight as a function of height, is near normal, body fat mass is increased in persons with SCI,[118–120] that is, persons with SCI who do not appear to be obese, carry relatively large amounts of fat tissue.[119] Although obesity is associated with increased risk of sleep apnea and lower functional skills, both obesity and increased body fat mass are associated with increased risk of diabetes mellitus, hypertension, cardiovascular disease, and so on. Increased body fat mass and obesity are related to physical inactivity and diet. It is not known if physical exercise can alter the body weight of persons with SCI, but it has been reported that FES-LCE training results in less fat infiltration between exercised muscle fibers as evident by imaging studies.[121]

Diabetes mellitus

Physical inactivity and obesity are recognized as major risk factors for diabetes mellitus,[122] which in turn is a risk factor for cardiovascular disease. Increased prevalence of glucose intolerance and diabetes among persons with SCI has been well documented,[123–125] which is not surprising given their sedentary lifestyle and increased body fat mass. It has been shown that peak serum glucose in persons with SCI is associated with increased total body percentage fat, complete tetraplegia, older age and male gender.[125] Physical activity, especially regular aerobic endurance exercise, has been shown to reduce the incidence and prevalence of diabetes in the general population[122,126] and among persons with SCI, it has been shown that following 8 weeks of FES-LCE training, blood glucose levels were significantly reduced and glucose utilization improved.[127]

Leg edema

Peripheral edema due to leg dependency, lack of muscle activity and poor venous return is clinically apparent in many persons with SCI. Such edema is generally felt to be harmless, although usually of considerable concern to the person affected. Leg edema as well as acrocyanosis of the feet have been reported to improve during FES-LCE training.[128,129]

Deep vein thrombosis

Venus thromboembolic disease is common and a leading cause of mortality following acute SCI. Predisposing factors include, venous stasis due to paralysis of leg muscles associated with failure of the venous muscle pump as well as changes in the clotting mechanism.[130] Simple electrical stimulation of leg muscles in combination with low dose heparin therapy has been shown to be superior to using only heparin to prevent deep vein thrombosis (DVT) in acute SCI.[131] Although DVT is relatively rare during the chronic stage of SCI, it may be speculated that regular leg exercise by FES-LCE might be helpful in preventing DVT, but no studies have been published that have addressed this issue.

Decreased muscle bulk, strength and endurance

Following SCI, the paralyzed muscles develop atrophy, even when spastic, and lose strength in response to electrical stimulation as well as ability to forcefully contract repetitively. In response to FES-LCE training, subjects with SCI have been shown to increase their thigh circumference as measured clinically by tape[17] or as visualized on CT or MRI imaging studies,[17,121,132] increase the resistance while pedaling the FES-LCE[17,105,106,133] and all gained endurance, that is, they could cycle for longer periods of time.[17,105,133] Muscle biopsy studies have shown a switch from myosin heavy chain (MHC) isoform II B muscle fibers (fast twitch, fast fatiguable and glycolytic fibers) to MHC isoform II fibers (fast twitch and fatigue resistant), with such exercise, which is accompanied by doubling of the mitochondrial oxidative capacity.[17] These studies have confirmed the reversibility of disuse changes in muscles paralyzed by spinal cord UMN lesions.

Pressure ulcers

It is well known that persons with SCI are at a high risk and frequently develop pressure ulcers at any time during their lives. Pulsed electrical stimulation has been shown to facilitate healing of stage II, III and IV pressure ulcers[134,135] and is recommended for that purpose by the Agency for Healthcare Research and Quality.[136] Electric muscle stimulation for prevention of pressure ulcers has been suggested based on research which showed that such stimulation of the gluteus maximus muscle produces increased muscle blood flow and undulation of the buttock tissues, that is muscle contraction and relaxation, with shape refiguration,[137,138] effects which are in addition to the well-documented and potentially protective increase in muscles bulk with such intervention. It is not known how effective FES-LCE is in prevention of pressure ulcers but none of the published reports on this intervention has reported development of pressure ulcers during the training period. An anecdotal report describes the healing of pressure ulcer during FES-LCE when traditional wound care seemed ineffective.[139]

Osteoporosis

Immediately following SCI, bone resorption occurs at a faster rate than bone formation, a process that results in clinical osteoporosis within a few weeks of injury.[140,141] Normal bone remodeling rate, that is, resorption equals formation, is re-established in 1–2 years after SCI, but by then loss of approximately one-third of the original bone mass has occurred.[140] This bone loss remains constant throughout the life of the individual and is associated with increased risk of fractures. No effective intervention to prevent or to restore bone loss after SCI is currently known. However, as the cause of such bone loss after SCI is felt to be related to the paralysis and disuse, it has been speculated that reversal of bone loss may occur with weight-bearing activities[142,143] and with FES-LCE training. Most studies have failed to show any significant increase in bone mineral density with FES-LCE training[144,145] or by lower limb FES ambulation (Parastep),[146] whereas other investigators have shown that FES-LCE can restore tibial bone mass by 10–30%.[147,148]

Depression

Mood disorders, such as depression and anxiety, are common after SCI and are present in as many as 30% for 2 or more years after injury.[149] Risk factors are felt to be similar to those in able-bodied persons, as well as the extent of the neurological impairment and the presence of medical comorbidities.[150] It has been well documented that there may be an inverse association between physical inactivity and mental health in both men and women[151] and that physical exercise has significant antidepressive effect[152–155] and may even improve cognitive function. It is known that SCI disturbs the hypothalamic–pituitary–adrenal axis,[156,157] which affects production of various hormones, including neuroendocrine stress hormones, for example, cortisol, growth hormone, endorphins and norepinephrine. After SCI, production of ACTH and cortisol does not follow normal circadian rhythm[156] and endorphin levels have been shown to be low,[158] both findings that may be associated with depression. One study on persons with SCI showed that with regular FES-LCE endorphin production increased, baseline cortisol levels became better regulated and closer to normal circadian rhythmicity and depression scores improved,[158] whereas another study showed that majority of participants reported improvement in self image and perceived appearance.[128]

Impaired neural plasticity

CNS plasticity refers to the CNS ability to change its structure and function in response to environmental stimuli, such as physical exercise. Undamaged spinal cord circuits have been shown to be capable of significant reorganization which may be induced by both activity-dependent and injury-induced plasticity.[159] Both clinical and animal studies have shown that physical exercise is beneficial for neuronal function[160,161] as clinically evident by better cognitive function.[160,162] Animal studies have found that exercise elevates the levels of neurotrophic factors in select regions of the adult brain and spinal cord,[9] including levels of insulin-like growth factor,[163] fibroblast growth factor II[164] and BDNF.[165] Several clinical investigators have shown that in persons with incomplete SCI walking ability may be improved with FES-LCE training,[166–168] BWSTT[169–171] or combinations thereof[63] or overground mobility therapy.[172] Other investigators have suggested that patterned neuronal activity with FES and/or BWSTT is important for development and even recovery of neurological functions[8] or by using both BWSTT and epidural spinal cord stimulation.[7,173] In general, it is now felt that the functional motor benefits of such exercise training does more than improve muscle strength and cardiovascular fitness in persons with SCI as animal studies have shown that it may also have an influence on synapses and motor neurons.[174] If and when a treatment will be found to reverse the neurological loss after SCI, it is unlikely that such treatment will result in complete reestablishment of all the descending and ascending projections within the spinal cord. Therefore, it will probably be necessary to activate the CNS plasticity, including neural circuitry within the spinal cord to maximize locomotor recovery through exercise training, such as FES and BWSTT.

The future for FES

The earliest observations of the use of FES to overcome paralysis were published almost 50 years ago.[25,42,175] Since that time, the spectacular technological advances in electronics and microprocessing have enabled scientists to develop a variety of FES systems that have been shown to have significant clinical benefits for their users. However, commercial success has been limited for several reasons, including the relatively small market, high cost of FES systems and their implantation, reluctant third-party payors, technological shortcomings, lack of totally implantable FES systems, insufficient clinical trials to scientifically document benefits, including reduced cost of care.

Several of these concerns are currently being addressed by scientists in the field of FES[11] who plan to use state-of-the-art electronics to miniaturize all components of FES systems and to create long-lasting implanted miniaturized batteries that can be recharged transcutaneously by radiofrequency transmission. Investigators are addressing the imminent need to develop a totally implantable, easily manufactured, modular FES system that can be used for all purposes, for example, for upper and lower limbs, trunk, bladder, bowel and diaphragmatic functions. Such system will be upgradeable to provide additional and advanced functions by adding different components, for example, stimulator and sensor modules. Implantation early after SCI using less-invasive surgical techniques would make such FES systems a clinical option during acute rehabilitation. Reconstructive hand surgery in combination with implantation of FES system may enable more persons with tetraplegia to achieve greater hand function. Judicious application of orthoses similarly may enhance functional performance of many users of FES systems.

More futuristic scientific developments include the potential use of high-frequency alternating currents to create a

quickly reversible nerve conduction block,[104] which may eliminate the need for posterior rhizotomy, which is often needed for bladder FES systems, as well as to suppress contractions of a hyperactive bladder, control pain, and so on. Such conduction block appears to be more achievable in nerve fibers of large diameter, for example motor fibers, than those of small diameter, for example sensory fibers. If electrical stimulation could be used to both activate and inhibit nerve and muscle activity, the clinical benefits of FES systems could be significantly increased.[11]

Advanced methods to control FES systems have been proposed,[11] and in some cases implemented, including the use of myoelectric signals from voluntary muscle contractions and sophisticated closed loop systems that automatically adjust stimulation patterns based on feedback from peripherally placed sensors.[176] It has been shown that epidural spinal cord stimulation in conjunction with BWSTT can facilitate functional walking in persons with chronic SCI ASIA C, perhaps by eliciting greater activation of the oxidative motor unit pool.[7,173] Other investigators have shown in animal experiments that stimulation of motor neuron pools within the gray matter of the spinal cord by implanted microelectrode arrays can activate large number of individual muscle fibers in a relatively coordinated pattern.[177,178] These observations suggest that it may be possible to activate by electrical stimulation the natural neural circuitry in the spinal cord to generate functional muscle activity.[11]

Perhaps the greatest attention in recent years has been paid to research which aims to enable persons with tetraplegia to control their environment by thought.[179–181] Recently, investigators have shown that a persons with C4 ASIA A tetraplegia and a 96 microelectrode array surgically implanted on the surface of the primary motor center area of the brain was able to modulate cortical spiking patterns by intended hand motion and use such neural control to open simulated e-mail, operate devices such as television, open and close a prosthetic hand, and perform rudimentary actions with multi-jointed robotic arm.[182] Such thought created brain signals may ultimately allow persons with SCI to create reliable commands and control FES systems by thought, rather than by the current methods which rely on external joint angle sensors, accelerometers and switches operated by voluntary muscle power.[11]

Conclusions

At present, creative transfer of the vast available technology in microelectronics to benefit persons with SCI appears to be a swifter way to enhance their function, quality of life, and community reintegration, than by waiting for science to find methods to regenerate axons within the injured spinal cord. With relatively limited research funding, development of FES systems has rapidly advanced by using recent technological developments, particularly those of advanced materials, implantable rechargeable batteries, wireless communication and miniaturization of electronics. These systems have been shown to be of great clinical value to several select groups of persons with SCI. People with C5–6 tetraplegia have become able to open their hands, grasp, hold and release objects. Those with T1–T12 paraplegia have become able to stand, step and adjust their body positions. Ventilatory dependent persons with tetraplegia at C3 and above have achieved ventilatory free breathing and persons with neurogenic bladder and intact S2–S4 LMN have been able to maintain urinary continence and effectively evacuate the bladder and even the bowel. Regular active physical exercise of the paralyzed lower limbs by FES-LCE has been shown to have numerous health-related benefits. Development of miniature modular FES systems, totally implantable by minimally invasive surgical techniques, are likely to simplify the application of this clinical process and may ultimately make FES technology a standard of care for many persons with SCI, reduce their total cost of care and enhance their quality of life. Enlarging the market for FES systems beyond SCI is likely to drive down prices that in combination with reduced cost of care may encourage third-party payors to more readily reimburse its cost.

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References

1 Thomas EL. Nursing care of the patient with spinal cord injury. In: Pierce DS, Nickel VH (eds). *The Total Care of Spinal Cord Injuries*. Little Brown and Company: Boston, MA, 1977, pp 249–297.
2 Spinal Cord Injury. *Facts and Factors at a Glance, Birmingham, Alabama*. National Spinal Cord Injury Statistical Center, Birmingham, Alabama, 2006.
3 Fiedler IG, Laud PW, Maiman DJ, Apple DF. Economics of Managed Care in Spinal Cord Injury. *Arch Phys Med Rehabil* 1999; **80**: 1441–1449.
4 DeVivo MJ. Epidemiology of Traumatic Spinal Cord Injury. In: Kirshblum S, Campagnolo DI, DeLisa JA (eds). *Spinal Cord Medicine*. Lippincott, Williams and Wilkins: Philadelphia, 2002, pp. 69–81.
5 Kakulas BA. Neuropathology: the foundation for new treatments in spinal cord injury. *Spinal Cord* 2004; **42**: 549–563.
6 Brandt EN, Pope AM (eds). Assessing the role of rehabilitation science and engineering. *Enabling America*. National Academy Press: Washington, DC, 1997.
7 Herman R, He J, D'Luzansky S, Willis W, Dilli S. Spinal cord stimulation facilitates functional walking in a chronic incomplete spinal cord injured. *Spinal Cord* 2002; **40**: 65–68.
8 McDonald JW, Becker D, Sadowsky CL, Jane JA, Conturo TE, Schultz LM. Late recovery following spinal cord injury: case report and review of the literature. *J Neurosurg (Spine 2)* 2002; **97**: 252–265.
9 Vaynman S, Gomez-Pinella F. License to run: exercise impacts functional plasticity in the intact and injured central nervous system by using neurotrophins. *Neurorehab Neural Repair* 2005; **19**: 283–295.

10 Peckham PH. Principles of electrical stimulation. *Top Spinal Cord Inj Rehabil* 1999; **5**: 1–5.
11 Peckham PH, Knutson JS. Functional electrical stimulation for neuromuscular applications. *Ann Rev Med Eng* 2005; **7**: 4.1–4.34.
12 Gorman PH, Mortimer JT. The effect of stimulus parameters on the recruitment characteristics of direct nerve stimulation. *IEEE Trans Biomed Eng* 1983; **30**: 407–414.
13 Peckham PH, Gorman PH. Functional electrical stimulation in the 21st century. *Topics Spinal Cord Inj Rehabil* 2004; **10**: 126–150.
14 Peckham PH, Mortimer JT, Marsolais EB. Alterations in the force and fatigability of skeletal muscle in quadriplegic humans following exercise induced by chronic electrical stimulation. *Clin Orthop* 1976; **114**: 326–334.
15 Lieber RL. Comparison between animal and human studies of skeletal muscle adaptation to chronic stimulation. *Clin Orthop* 1988; **233**: 19–24.
16 Salmons S, Henriksson J. The adaptive response of skeletal muscle to increased use. *Muscle Nerve* 1981; **4**: 94–105.
17 Mohr T, Andersen JL, Biering-Sorensen F, Galbo H, Bangsbo J, Wagner A *et al*. Long term adaptation to electrically induced cycle training in severe spinal cord injured individuals. *Spinal Cord* 1997; **35**: 1–16.
18 Ragnarsson KT, Baker LL. Functional Electrical Stimulation in persons with spinal cord injury. In: Gonzalez EG, Myers SJ, Edelstein AE, Lieberman JS, Downey JA (eds). *Physiological Basis of Rehabilitation Medicine*. Butterworth-Heinemann: Boston, 2001, pp. 723–745.
19 Knutson JS, Naples GG, Peckham PF, Keith MW. Electrode fracture rates and occurrences of infection and granuloma associated with percutaneous intramuscular electrodes in upper limb functional electrical stimulation applications. *J Rehabil Res Devel* 2002; **39**: 671–684.
20 Kilgore KL, Peckham PH, Keith MW, Montague FW, Hart RL, Gazdik MM *et al*. Durability of implanted electrodes and leads in upper limb neuroprosthesis. *J Rehabil Res Devel* 2003; **40**: 457–468.
21 Uhlir JP, Triolo RJ, Davis Jr JA, Bieri C. Performance of epimysial stimulating electrodes in the lower extremities of individuals with spinal cord injury. *IEEE Trans Syst Rehabil Eng* 2004; **12**: 279–287.
22 Loeb GE, Walmsley B, Duysens J. Obtaining proprioceptive information from natural limbs: implantable transducers vs. somatosensory neuron recordings. In: Newman MR, Fleming DG, Cheung PW, Ko WH (eds). *Solid State Physical Sensors for Biomedical Applications*. Boca Raton, Florida, CRC, 1980.
23 Petrofsky JS, Phillips CA, Stafford DE. Closed Loop Control for restoration of movement in paralyzed muscles. *Orthopaedics* 1984; **7**: 1289–1302.
24 Bryden AM, Kilgore KL, Kirsch RF, Memberg WD, Peckham PH, Keith MW. An implanted neuroprosthesis for high tetraplegia. *Top Spinal Cord Inj Rehabil* 2005; **10**: 38–52.
25 Long C, Masciarelli VD. An Electophysiologic Splint for the Hand. *Archives Phys Med Rehabil* 1963; **44**: 499–503.
26 Alon G, McBride K. Persons with C5 or C6 tetraplegia achieve selected functional gains using a neuroprosthesis. *Arch Phys Med Rehabil* 2003; **84**: 119–124.
27 Knutson J, Audu M, Triolo R. Interventions for mobility and manipulation after spinal cord injury: a review of orthotic and neuroprosthetic options. *Top Spinal Cord Inj Rehabil* 2006; **11**: 61–81.
28 Popovic MR, Popovic DB, Keller T. Neuroprosthesis for grasping. *Neurol Res* 2002; **24**: 443–452.
29 Keith MS, Peckham PH, Thrope GB, Stroh KC, Smith B, Burkett JR *et al*. Implantable functional neuromuscular stimulation in the tetraplegic hand. *J Hand Surg* 1989; **14A**: 524–530.
30 Peckham PH, Keith MW, Kilgore KL, Grill JH, Wuolle KS, Thrope GB *et al*. Efficacy of an implanted neuroprosthesis for restoring hand grasp in tetraplegia: a multi-center study. *Arch Phys Med Rehabil* 2001; **82**: 1380–1388.
31 Taylor P, Esnouf J, Hobby J. The functional impact of the Freehand system on tetraplegic hand function. Clinical results. *Spinal Cord* 2002; **40**: 560–566.
32 Peckham PH, Kilgore K, Keith MW, Bryden AM, Bradra N, Montague FW. An advanced neuroprosthesis for restoration of hand and upper arm control using an implantable controller. *J Hand Surg* 2002; **27A**: 265–276.
33 Peckham PH, Keith MW, Freehafer AA. Restoration of functional control by electrical stimulation in the upper extremity of the quadriplegic patient. *J Bone Joint Surg* 70A; **144–148**: 1988.
34 Keith MW, Peckham PH, Thrope GB, Stroh KC, Smith B, Buckett JR *et al*. Functional neuromuscular stimulation neuroprosthesis for the tetraplegic hand. *Clin Orthop* 1988; **233**: 25–33.
35 Mulcahey MJ, Betz RR, Kozin SH, Smith BT, Hutchinson D, Lutz C. Implantation of the Freehand system during initial rehabilitation using minimally invasive techniques. *Spinal Cord* 2004; **42**: 146–155.
36 Waters RL, Muccitelli LM. Tendon transfers to improve function of patients with tetraplegia. In: Kirshblum S, Campagnolo DI, DeLisa JA (eds). *Spinal Cord Medicine*, Chapter 28, Lippincott, Williams and Wilkins: Philadelphia, 2002, pp 424–437.
37 Keith MW, Kilgore KL, Peckham PH, Wuolle KS, Creasey G, Lemay M. Tendon transfers and functional electrical stimulation for restoration of hand function in spinal cord injury. *J Hand Surg* 1996; **21A**: 89–99.
38 Memberg WD, Crago PE, Keith MW. Restoration of elbow extension via functional electrical stimulation in individuals with tetraplegia. *J Rehabil Res Develop* 2003; **40**: 477–486.
39 Peckham PH, Kilgore KL, Keith MW, Bryden AM, Bhadra N, Montague FW. An advanced neuroprosthesis for restoration of hand and upper arm control using an implantable controller. *J Hand Surg* 2002; **27A**: 265–276.
40 Bryden AM, Kilgore KL, Kirsch RF, Memberg WD, Peckham PH, Keith MW. An implanted neuroprosthesis for high tetraplegia. *Topics Spinal Cord Inj Rehabil* 2005; **10**: 38–52.
41 Keith MW, Hoyen H. Indications and future directions for upper limb neuroprosthesis in tetraplegic patients: a review. *Hand Clin* 2002; **18**: 519–528.
42 Kantrowitz A. *Electronic Physiologic Aids*. Maimonides Hospital: Brooklyn, New York, 1960, pp 4–5.
43 Davis JA, Triolo RJ, Uhlir JP, Bieri C, Rohde L, Lissy D *et al*. Preliminary performance of a surgically implanted neuroprosthesis for standing and transfers. *J Rehabil Res Devel* 2001; **38**: 609–617.
44 Solomonow M. Biomechanics and physiology of practical function on neuromuscular stimulation powered walking orthosis for paraplegics. In: Stein RB, Peckham PH, Popovic DP (eds). *Neural Prostheses: Replacing Motor Function after Disease or Disability*. Oxford University Press: New York, 1992, pp 202–232.
45 Marsolais EB, Kobetic R, Polando G, Ferguson K, Tashman S, Gaudio R *et al*. The Case Western Reserve University Hybrid Gait Orthosis. *J Spinal Cord Med* 2000; **23**: 100–108.
46 Kralj A, Bajd T, Turk R. Electrical stimulation providing functional use of paraplegia patient muscles. *Med Prog Technol* 1980; **7**: 3–9.
47 Bajd T, Kralj A, Turk R, Benko H, Sega J. The use of a four-channel electrical stimulator as an ambulatory aid for paraplegic patients. *Phys Ther* 1983; **63**: 1116–1120.
48 Graupe D, Kohn KH. *Functional Electrical Stimulation for Ambulation by Paraplegics: 12 Years of Clinical Observations and System Studies*. Kreger Publishing Company: Malibar, Florida, 1994.
49 Klose KJ, Jacobs PL, Broton JG, Guest RS, Needham-Shropshire RM, Lebwohl N *et al*. Evaluation of a training program for persons with SCI paraplegia using the Parastep I ambulation system: Part 1. Ambulation performance and anthropometric measures. *Arch Phys Med Rehabil* 1997; **78**: 789–793.
50 Brissot R, Gallien P, LeBot MP, Beaubras A, Laisene D, Beillot J *et al*. Clinical experience with functional electrical stimulation assisted gait with parastep in spinal cord injured patients. *Spine* 2000; **25**: 501–508.
51 Marsolais EB, Kobetic R. Functional electrical stimulation for walking in paraplegia. *J Bone Joint Surg* 1987; **69A**: 728–733.
52 Kobetic R, Marsolais EB. Synthesis of Paraplegic Gait with multichannel functional neuromuscular stimulation. *IEEE Trans Rehabil Engin* 1994; **2**: 66–79.

53 Rushton DN, Donaldson ND, Barr FM, Harper BJ, Perkins TA, Taylor PN *et al*. Lumbar root stimulation for restoring leg function: results in paraplegia. *Artific Org* 1997; **21**: 180–182.
54 Davis R, Patrick J, Barriskill A. Development of functional electrical stimulators using cochlear implant technology. *Med Eng Phys* 2001; **23**: 61–68.
55 Kobetic R, Triolo RJ, Uhlir JP, Bieri C, Wibowo M, Polando G *et al*. Implanted functional electrical stimulation system for mobility in paraplegia: a follow-up case report, IEEE Trans. *Rehabil Eng* 1999; **7**: 390–398.
56 Wilkenfeld AJ, Audu ML, Triolo RJ. Feasibility of functional electrical stimulation for control of seated posture after spinal cord injury: a simulation study. *J Rehabil Res Devel* 2006; **43**: 139–152.
57 Solomonow M, Aguilar E, Reisin E, Baratta RV, Best R, Coetzee T *et al*. Reciprocating gait orthosis powered with electrical muscle stimulation (RGO II). Part 1: performance evaluation of 70 paraplegic patients. *Orthopaedics* 1997; **20**: 315–324.
58 Solomonow M, Reisin E, Aguilar E, Baratta RV, Best R, Coetzee T *et al*. Reciprocal gait orthosis powered with electrical muscle stimulation (RGO II). Part 2: medical evaluation of 70 paraplegic patients. *Orthopaedics* 1997; **20**: 411–418.
59 Douglas R, Larsen PF, D'Ambrosia R, McCall RE. The LSU reciprocating gait orthosis. *Orthopaedics* 1983; **6**: 834–839.
60 Marsolais EB, Edwards BG. Energy costs of walking and standing with functional neuromuscular stimulation and long leg braces. *Arch Phys Med Rehabil* 1988; **69**: 243–249.
61 Petrofsky JS, Smith JB. Physiologic cost of computer controlled walking in persons with paraplegia using a reciprocating gait orthosis. *Arch Phys Med Rehabil* 1991; **72**: 890–896.
62 Nene AV, Patrick JH. Energy cost of paraplegic locomotion using the parawalker-electrical stimulation 'hybrid' orthosis. *Arch Phys Med Rehabil* 1990; **71**: 116–120.
63 Field-Fote EC. Combined use of body weight support, functional electric stimulation and treadmill training to improve walking ability in individuals with chronic incomplete spinal cord injury. *Arch Phys Med Rehabil* 2001; **82**: 818–824.
64 Hesse S, Werner C, Bardeleben A. Electromechanical gait training with functional electrical stimulation: case studies in spinal cord injury. *Spinal Cord* 2004; **42**: 346–352.
65 Hicks AL, Adams MM, Ginis KM, Giangregorio L, Latimer A, Phillips SM *et al*. Long-term-body-weight-supported treadmill training and subsequent follow-up in persons with chronic SCI: effects on functional walking ability and measures of subjective well-being. *Spinal Cord* 2005; **43**: 291–298.
66 Carter RE, Menter R, Wood M, Wilmot C, Hall K. Available respiratory options. In: Whiteneck G, Adler C, Carter RE *et al*. (eds). *The Management of High Quadriplegia*, Chapter 12. Demos Publications: New York, NY, 1989, pp. 166–168.
67 Baer GA, Talonen PP, Hakkinen V, Exner G, Yrjola H. Phrenic nerve stimulation in tetraplegia. A new regiment to condition the diaphragm for full time respiration. *Scand J Rehabil Med* 1990; **22**: 107–111.
68 Creasey G, Elefteriades J, DiMarco A, Tallinan P, Bijak M, Girsch W *et al*. Electrical stimulation to restore respiration. *J Rehabil Res and Devel* 1996; **33**: 123–132.
69 Chervin RD, Guilleminault C. Diphragm pacing: review and reassessment. *Sleep* 1994; **17**: 176–187.
70 DiMarco AF, Onders RP, Kowalsky KE, Miller ME, Ferek S, Mortimer JT. Phrenic nerve pacing in a tetraplegic patient via intramuscular diaphragm electrodes. *Am J Respira Crit Care Med* 2002; **166**: 1604–1606.
71 Onders RP, DiMarco AF, Ignani AR, Aiyar H, Mortimer JT. Mapping of the phrenic nerve motor point: the key to a successful laparoscopic diaphragm pacing system in the first human series. *Surgery* 2004; **136**: 819–826.
72 DiMarco AF, Onders RP, Ignani AR, Kowalsky KE, Mortimer JT. Phrenic nerve pacing via intramuscular diaphragm electrodes in tetraplegic subjects. *Chest* 2005; **127**: 671–678.
73 DiMarco AF, Onders RP, Ignani A, Kowalski KE. Inpiratory muscle pacing in spinal cord injury: case report and clinical commentary. *J Spinal Cord Med* 2006; **29**: 95–108.
74 Mayr W, Bijak M, Girsch W, Holle J, Lanmuller H, Thoma H *et al*. Multichannel stimulation of phrenic nerves by epineural electrodes: clinical experience and future developments. *Trans Am Soc Artific Int Org J* 1993; **39**: M729–M735.
75 Glenn WW, Holcomb WG, McLaughlin AJ, O'Hare JM, Hogan JF, Yasuda R. Total ventilatory support in a quadriplegic patient with radio-frequency electrophrenic respiration. *New Engl J Med* 1972; **286**: 513–516.
76 Glenn WW, Holcomb WG, Shaw RK, Hogan JF, Holschuh KR. Long term ventilatory support by diaphragm pacing in quadriplegia. *Ann Surg* 1976; **183**: 566–577.
77 Glenn WW, Phelps ML, Elefteriades JA, Dentz B, Hogan JF. Twenty years of experience in phrenic nerve stimulation to pace the diaphragm. *Pacing Clin Electrophysiol* 1986; **9**: 780–784.
78 Dobelle WH, D'Angelo MS, Goetz BF, Kieter DG, Lallier TJ, Lamb JI *et al*. Two hundred cases with a new breathing pacemaker dispels myths about diaphragm pacing. *Trans Am Soc Artific Int Org* 1994; **40**: 244–252.
79 Glenn WW, Brouillette RT, Dentz B, Fodstad H, Hunt CE, Keens TG *et al*. Fundamental considerations in pacing of the diaphragm for chronic ventilatory insufficiency: a multi-center study. *Pacing Clinical Electrophysiology* 1988; **11**: 2121–2127.
80 Weese-Mayer EE, Silvestri JM, Kenny AS. Diaphragm pacing with quadripolar phrenic nerve electrode: an international study. *Pacing Clin Electrophysiol* 1996; **19**: 1311–1319.
81 Krieger AJ, Gropper MR, Adler RJ. Electrophrenic respiration after intercostal phrenic nerve anastomosis in a patient with anterior spinal artery syndrome: technical case report. *Neurosurgery* 1994; **35**: 760–763.
82 Linder SH. Functional electrical stimulation to enhance cough in quadriplegia. *Chest* 1993; **103**: 166–169.
83 Jaeger RJ, Turba RM, Yarkony GM, Roth EJ. Cough in spinal cord injured patients: comparison of three methods to produce cough. *Arch Phys Med Rehabil* 1993; **74**: 1358–1361.
84 DiMarco FR, Romaniuk JR, Supinski GS. Electrical activation of the expiratory muscles to restore cough. *Am J Respir Crit Care Med* 1995; **151**: 1466–1471.
85 Lin VWH, Singh H, Chitkara RK, Perkash I. Functional magnetic stimulation for restoring cough in patients with tetraplegia. *Arch Phys Med Rehabil* 1998; **79**: 517–522.
86 Budge J. ber Der Einfluss Des Nervensystems Auf Die Bewegung Der Blase. *Zep Rationelle Medicine* 21; **1**: 1854.
87 Brindley GS. Electrode-arrays for making long-lasting electrical connection to spinal roots. *J Physiol* 1972; **222**: 135–136.
88 Brindley GS, Polkey CE, Rushton DN, Cardozo L. Sacral anterior root stimulators for bladder control in paraplegia: the first 50 cases. *J Neurol, Neurosurg Psychiatr* 1986; **49**: 1104–1114.
89 Brindley GS. The first 500 patients with sacral anterior stimulator implants: general description. *Paraplegia* 1994; **32**: 795–805.
90 Brindley GS, Polkey CE, Rushton DN. Sacral anterior root simulators for bladder control in paraplegia. *Paraplegia* 1982; **20**: 365–381.
91 Creasey GH, Ho CH, Triolo RJ, Gater DR, DiMarco AF, Bogie KM *et al*. Clinical applications of electrical stimulation after spinal cord injury. *J Spinal Cord Med* 2004; **27**: 365–375.
92 Madersbacher H, Fischer J. Anterior sacral root stimulation and posterior sacral root rhizotomy. *Akta Urologica* 1993; **24** (Suppl): 32–35.
93 Creasey GH, Grill JH, Korsten M, Hoi Sang U, Betz R, Anderson R *et al*. An implantable neuroprosthesis for restoring bladder and bowel control in patients with spinal cord injuries: a multi-center trial. *Arch Phys Med Rehabil* 2001; **82**: 1512–1519.
94 Brindley GS. The first 500 sacral anterior root stimulators: implant failures and their repair. *Paraplegia* 1995; **33**: 5–9.
95 Varma JS, Binnie N, Smith AN, Creasey GH, Edmond P. Differential effects of sacral anterior root stimulation on anal sphincter and colorectal mortility in spinally injured man. *Br J Surg* 1986; **73**: 478–482.
96 MacDonagh RP, Sun WM, Smallwood R, Forster D, Read NW. Control of defecation in patients with spinal injuries by stimulation of sacral anterior nerve roots. *B MJ* 1990; **300**: 1494–1497.

97 Binnie N, Smith A, Creasey GH, Edmond P. The effects of electrical anterior sacral nerve root stimulation on pelvic floor function in paraplegic subjects. *J Gastrointest Motility* 1991; **3**: 39–45.
98 Brindley GS. Neuroprosthesis used to restore male sexual or reproductive function. *Baillieres Clin Neurol* 1995; **4**: 15–20.
99 Biering-Sorensen F, Sonksen J. Sexual function in spinal cord lesion men. *Spinal Cord* 2001; **39**: 456–470.
100 Brindley GS, Sauerwein D, Hendry WF. Hypogastric plexus stimulators for obtaining semen from paraplegic men. *Br J Urol* 1989; **64**: 72–77.
101 Vodusek DB, Light KJ, Libby JM. Detrusor inhibition induced by stimulation of pudendal nerve afferents. *Neurourol Urodyn* 1986; **5**: 381–389.
102 Craggs MD, McFarlane JP. Neuromodulation of the lower urinary tract. *Exper Physiol* 1999; **84**: 149–160.
103 Kirkham APS, Knight SL, Craggs MD, Casey ATM, Shah PJR. Neuromodulation through sacral nerve roots 2 to 4 with a Finetech–Brindley sacral posterior and anterior root simulator. *Spinal Cord* 2002; **40**: 272–281.
104 Kilgore KL, Bhadra N. Nerve conduction block utilizing high-frequency alternating current. *Med Biol Eng Comput* 2004; **42**: 394–406.
105 Ragnarsson KT, Pollack S, O'Daniel W, Edgar R, Petrofsky J, Nash MS. Clinical evaluation of computerized functional electrical stimulation after spinal cord injury: A multi-center pilot study. *Arch Phys Med Rehabil* 1988; **69**: 672–677.
106 Pollack SF, Axen K, Spielholz N, Levin N, Haas F, Ragnarsson KT. Aerobic training effects of electrically induced lower extremity exercises in spinal cord injured people. *Arch Phys Med Rehabil* 1989; **70**: 214–219.
107 Hooker SP, Figoni SF, Glaser RM, Rodgers MM, Ezenwa BN, Faghri PD. Physiological responses to prolonged electrically stimulated leg cycle exercise in the spinal cord injured. *Arch Phys Med Rehabil* 1990; **71**: 863–869.
108 Hooker SP, Figoni SF, Rogers MM, Glaser RM, Mathews T, Suryaprasad AG *et al*. Physiologic effects of electrical stimulation leg cycle exercise training in spinal cord injured persons. *Arch Phys Med Rehabil* 1992; **73**: 470–476.
109 Hooker SP, Scremin E, Mutton DL, Kunkel CF, Cagle G. Peak and submaximal physiologic responses following electrical stimulation leg cycle ergometer training. *J Rehabil Res Devel* 1994; **32**: 361–366.
110 Brenes G, Dearwater S, Shapera R, LaPorta RE, Collins E. High density lipoprotein cholesterol concentration in physically active and sedentary spinal cord patients. *Arch Phys Med Rehabil* 1986; **67**: 445–450.
111 Bauman WA, Spungen AM, Zhong YG, Rothstein JL, Petry C, Gordon SK. Depressed serum high density lipoprotein cholesterol levels in veterans with spinal cord injury. *Paraplegia* 1992; **30**: 697–703.
112 Bauman WA, Spungen AM. Disorders of carbohydrate and lipid metabolisms in veterans with paraplegia or quadriplegia: a model of premature aging. *Metabolism* 1994; **43**: 749–756.
113 Dallmeijer AJ, van der Woude LHV, vanKamp GJ, Hollander AP. Changes in lipid lipoprotein and appolipoprotein profiles in persons with spinal cord injuries during the first two years post injury. *Spinal Cord* 1999; **37**: 96–102.
114 Hartung GH. Physical activity and high density lipoprotein cholesterol. *J Sports Med Phys Fitness* 1995; **35**: 1–5.
115 Bauman WA, Adkins RH, Spungen AM, Kemp BJ, Waters Rl. The effect of residual neurological deficit on serum lipoproteins in individuals with chronic spinal cord injury. *Spinal Cord* 1998; **36**: 13–17.
116 Nash MS, Jacobs PL, Mendez AJ, Goldberg RC. Current resistance training improves the atherogenic lipid profiles of persons with chronic paraplegia. *J Spinal Cord Med* 2001; **24**: 2–9.
117 Szlachcic Y, Adkins RH, Adal T, Yee F, Bauman W, Waters RL. The effect of dietary intervention on lipid profiles in individuals with spinal cord injury. *J Spinal Cord Med* 2001; **24**: 26–29.
118 Gupta N, Whyte KT, Sanford PR. Body mass index in spinal cord injury – a retrospective study. *Spinal Cord* 2006; **44**: 92–94.
119 Jones LM, Legge M, Goulding A. Healthy body mass index values often underestimate body fat in men with spinal cord injury. *Arch Phys Med Rehabil* 2003; **84**: 1068–1071.
120 Rasmann-Nuhlicek DN, Spurr GB, Barboriak JJ, Rooney CB, Ghatit AZE, Bongard RD. Body composition of patients with spinal cord injury. *Eur J Clin Nutr* 1988; **42**: 765–773.
121 Ragnarsson KT. Physiologic effects of functional electrical stimulation induced exercises in spinal cord injured individuals. *Clin Orthopaedics* 1988; **233**: 53–63.
122 Helmrich SP, Ragland DR, Leung RW, Raffenbarger RS. Physical activity and reduced occurrence of non-insulin dependant diabetes mellitus. *N Engl J Med* 1991; **325**: 147–152.
123 Duckworth WC, Solomon SS, Jallepalli P, Heckemeyer C, Finnern J, Powers A. Glucose intolerance due to insulin resistance in patients with spinal cord injuries. *Diabetes* 1989; **29**: 906–910.
124 Bauman WA, Spungen AM. Disorders of carbohydrate and lipid metabolism in veterans with paraplegia or quadriplegia: a model of premature aging. *Metabolism* 1994; **43**: 749–756.
125 Bauman WA, Adkins RH, Spungen AM, Waters RL. The effect of residual neurological deficit on oral glucose tolerance in persons with chronic spinal cord injury. *Spinal Cord* 1999; **37**: 765–771.
126 Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CT. A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA* 1992; **268**: 63–67.
127 Jeon JY, Weiss CB, Steadward RD, Ryan E, Burnham RS, Bell G *et al*. Improved glucose tolerance and insulin sensitivity after electrical stimulation-assisted cycling in people with spinal cord injury. *Spinal Cord* 2002; **40**: 110–117.
128 Sipski ML, DeLisa JA, Schweer S. Functional Electrical stimulation bicycle ergometry: patient perceptions. *Am J Phys Med Rehabil* 1989; **68**: 147–149.
129 Twist DJ. Acrocyanosis in a spinal cord injured patient. The effects of computer controlled neuromuscular electrical stimulation: a Case report. *Phys Ther* 1990; **70**: 45–49.
130 Rossi E, Green D, Rosen J. Sequential changes in factor VIII and platelets proceeding deep vein thrombosis in patients with spinal cord injury. *Br J Hematol* 1980; **45**: 143–151.
131 Merli GJ, Herbison JG, Ditunno JF, Weitz HH, Henzes JH, Park CH *et al*. Deep vein thrombosis: prophylaxis in acute spinal cord injured patients. *Arch Phys Med Rehabil* 1988; **69**: 661–664.
132 Pacy PJ, Hesp R, Halliday DA, Katz D, Cameron G, Reeve J. Muscle and bone in paraplegic patients and the effect of functional electrical stimulation. *Clin Science* 1988; **75**: 481–487.
133 Sloan KE, Bremner LA, Byrne J, Day RE, Scull ER. Musculoskeletal effects of electrical stimulation induced cycling programme in the spinal injured. *Paraplegia* 1994; **32**: 407–415.
134 Griffin JW, Tooms RE, Mendius RA, Clift JK, VanderZwaag R, el-Zeky F. Efficacy of high voltage pulsed current for healing of pressure ulcers in patients with spinal cord injury. *Phys Ther* 1991; **71**: 433–443.
135 Feedar JA, Kloth LC, Gentzkow GD. Chronic dermal ulcer healing enhanced with monophasic pulsed electrical stimulation. *Phys Ther* 1991; **71**: 639–649.
136 Agency for Healthcare Policy and Research Treatment of Pressure Ulcers. Washington, DC, US Department of Health and Human Services, 1994.
137 Levine SP, Kett RL, Cederna PS, Brooks SV. Electric muscle stimulation for pressure sore prevention: tissue shape variation. *Arch Phys Med Rehabil* 1990; **71**: 210–215.
138 Levine SP, Kett RL, Gross MD, Wilson BA, Cederna PS, Juni JE. Blood flow in the gluteus maximus of seated individuals during electrical muscle stimulation. *Arch Phys Med Rehabil* 1990; **71**: 682–686.
139 Pollack SF, Ragnarsson KT, Dijkers M. The effect of electrically induced lower extremity ergometry on an ischial pressure ulcer: a case study. *J Spinal Cord Med* 2004; **27**: 143–147.
140 Garland DE, Stewart CA, Adkins RH, Hu SS, Rosen C, Liotta FJ *et al*. Osteoporosis after spinal cord injury. *J Orthop Res* 1992; **10**: 371–378.
141 Chen B, Stein A. Osteoporosis in acute spinal cord injury. *Top Spinal Cord Inj Rehabil* 2003; **9**: 26–35.

142 Kaplan PE, Gandhavadi B, Richards L, Goldschmidt J. Calcium balance in paraplegic patients: Influence of injury duration and ambulation. *Arch Phys Med Rehabil* 1978; **59**: 447–450.
143 Kaplan PE, Roden W, Gilbert E, Richards L, Goldschmidt JW. Reduction of hypercalcuria in tetraplegia after weight bearing and strengthening exercises. *Paraplegia* 1981; **19**: 289–293.
144 Leeds EM, Klose KJ, Ganz W, Serafini A, Green BA. Bone mineral density after bicycle ergometry training. *Arch Phys Med Rehabil* 1990; **71**: 207–209.
145 Bedell KK, Scremin AN, Perell KL, Kunkel CF. Effects of functional electrical stimulation induced lower extremity cycling on bone density of spinal cord injured patients. *Am J Phys Med Rehabil* 1996; **75**: 29–34.
146 Needham-Shropshire BM, Broton JG, Klose KJ, Lebwohl N, Guest RS, Jacobs PL. Evaluation of a training program for persons with SCI paraplegia using the Parastep I ambulation system: Part III. Lack of effect on bone mineral density. *Arch Phys Med Rehabil* 1997; **78**: 799–803.
147 Mohr T, Podenphant J, Biering-Sorensen F, Galbo H, Thamsborg G, Kjaer M. Increased bone mineral density after prolonged electrical induced cycle training of paralyzed limbs in spinal cord injured man. *Calcific Tissue Int* 1997; **61**: 22–25.
148 Belanger M, Stein RB, Wheeler GD, Gordon T, Leduc B. Electrical stimulation: can it increase muscle strength and reverse osteopenia in spinal cord injured individuals. *Arch Phys Med Rehabil* 2000; **81**: 1090–1098.
149 Craig AR, Hancock KM, Dixon HG. A longitudinal investigation into anxiety and depression in the first two years following a spinal cord injury. *Paraplegia* 1994; **32**: 675–679.
150 Consortium for Spinal Cord Medicine. *Depression following spinal cord injury. A Clinical Practice Guideline for Primary Care Physicians*. Paralyzed Veterans of America: Washington, DC, 1998.
151 Galper DI, Trivedi MH, Barlow CE, Dunn AL, Kampert JB. Inverse association between physical inactivity and mental health in both men and women. *Med Sci Sports Exerc* 2006; **38**: 173–178.
152 Trivedi MH, Greer TL, Grannemann BD, Church TS, Galper DI, Sunderajan P *et al*. Exercise as an augmentation strategy for treatment of major depression. *J Psychiatr Pract* 2006; **12**: 2005–2013.
153 Sjosten N, Kivela SL. The effects of physical exercise on depressive symptoms among the aged: a systematic review. *Int J Geriatr Psychiatry* 2006; **21**: 410–418.
154 Ernst C, Olson AK, Pinel JP, Pinel JP, Lam RW, Christie BR. Antidepressant effect of exercise: evidence for an adult-neurogenesis hypothesis? *J Psychiatry Neurosci* 2006; **31**: 84–92.
155 Shirayama Y, Chen ACH, Nakagawa S, Russell Ds, Duman RS. Brain derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *J Neurosci* 2002; **22**: 3251–3261.
156 Claus-Walker J, Halstead LS. Metabolic and endocrine changes in spinal cord injury. III, less quanta of sensory input plus bedrest and illness. *Arch Phys Med Rehabil* 982; **63**: 628–631.
157 McDaniel JW, Sexton AW. Psychoendocrine functions in relation to level of spinal cord transsection. *Hormonal Behav* 1971; **2**: 56–96.
158 Twist DJ, Culpepper-Morgan JA, Ragnarsson KT, Petrillo CR, Creek MJ. Neuroendocrine changes during functional electrical stimulation. *Am J Phys Med Rehabil* 1992; **71**: 156–163.
159 Curt A, Schwab ME, Deitz V. Providing the clinical basis for new interventional therapies: refined diagnosis and assessment of recovery after spinal cord injury. *Spinal Cord* 2004; **42**: 1–6.
160 Kramer AF, Hahn S, Cohen MJ, Banich MT, McAuley E, Harrison CR *et al*. Aging, fitness and neurocognitive function. *Nature* 1999; **400**: 418–419.
161 Samorajski T, Delaney C, Durham L, Ordy JM, Johnson JA, Dunlap WP. Effect of exercise on longevity, body weight, locomotive performance and passive-avoidance memory of C57 BL/6J mice. *Neurobiol Aging* 1985; **6**: 17–24.
162 Laurin D, Verreoult R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol* 2001; **58**: 498–504.
163 Carro E, Trejo JL, Busiguina S, Torres-Aleman I. Circulating insulin like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. *J Neurosc* 2001; **21**: 5678–5684.
164 Gomez-Pinilla F, Dao L, So V. Physical exercise induces FGF-2 and its mRNA in the Hippocampus. *Brain Res* 1997; **764**: 1–8.
165 Neeper SA, Gomez-Pinilla F, Choi J, Cotman C. Exercise and brain neurotrophins. *Nature* 1995; **373**: 109.
166 Donaldson N, Perkins TA, Fitzwater R, Wood DE, Middleton F. FES cycling may promote recovery of leg function after incomplete spinal cord injury. *Spinal Cord* 2000; **38**: 680–682.
167 Johnston TE, Finson RL, Smith BT, Bonaroti DM, Betz RR, Mulcahey MJ. Functional electrical stimulation for augmented walking in adolescents with incomplete spinal cord injury. *J Spinal Cord Med* 2003; **26**: 390–400.
168 Thrasher TA, Flett HM, Popovic MR. Gait training regimen for incomplete spinal cord injury using functional electrical stimulation. *Spinal Cord* 2006; **44**: 357–361.
169 Dobkin BH, Harkema S, Requejo P, Edgerton VR. Modulation of locomotor like EMG activity in subjects with complete and incomplete spinal cord injury. *J Neurol Rehabil* 1995; **9**: 183–190.
170 Wernig A, Nanassy A, Muller S. Laufband (treadmill) therapy in incomplete paraplegia and tetraplegia. *J Neurotrauma* 1999; **16**: 719–726.
171 Postans HG, Hasler JP, Granat MH, Maxwell DJ. Functional electrical stimulation to augment partial weight-bearing supported treadmill training for patients with acute incomplete spinal cord injury: A pilot study. *Arch Phys Med Rehabil* 2004; **85**: 604–610.
172 Wernig A, Dobkin BH. Weight-supported treadmill vs. overground training for walking after acute incomplete spinal cord injury. *Neurol* 2006; **67**: 1900.
173 Ganley KJ, Willis WT, Carhart MR, He J, Herman RM. Epidural spinal cord stimulation improves locomotor performance in low ASIA C, Wheelchair dependant, spinal cord injured individuals: insights from metabolic response. *Top Spinal Cord Inj Rehabil* 2005; **11**: 50–63.
174 Mendell LM, Arvanian V, Petruska J. Treadmill step training after spinal cord injury influences synapses and motor neurons. 2006. Unpublished information from the International Research Consortium on Spinal Cord Injury.
175 Liberson WT, Holmquest HJ, Scot D, Dow A. Functional electrotherapy: stimulation of the perineal nerve synchronized with the swing phase of gait of hemiplegic patients. *Arch Phys Med Rehabil* 1961; **42**: 101–195.
176 Sinkjaer T, Haugland M, Inmann A, Hansen M, Nielsen KD. Biopotentials as command and feedback signals in functional electrical stimulation systems. *Med Eng Physiol* 2003; **25**: 29–40.
177 Prochaska A, Mushahvar V, Yakovenko S. Activation and coordination of spinal motor neuron pools after spinal cord injury. *Prog Brain Res* 2002; **137**: 109–134.
178 McCreery D, Pikov V, Lossinsky A. Arrays for chronic functional microstimulation of the lumbo-sacral spinal cord. *IEEE Trans Neural Syst Rehabil Eng* 2004; **12**: 195–207.
179 Donoghue JP. Connecting cortex to machines: recent advances in brain interfaces. *Nature Neurosci Suppl* 2002; **5**: 1085–1088.
180 Nicolelis MAL. Brain machine interfaces to restore motor function and probe neural circuits. *Nature Rev Neurosci* 2003; **4**: 417–422.
181 Schwartz AB. Cortical neural prosthetics. *Ann Rev Neurosci* 2004; **27**: 487–507.
182 Hochberg LR, Serruya MD, Friehs GM, Mukand JA, Saleh M, Caplan AH *et al*. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature* 2006; **442**: 164–171.
183 Creasey GH. Restoration of bladder, bowel and sexual function. *Top Spinal Cord Inj Rehabil* 1994; **5**: 21–32.