

## The BION devices: injectable interfaces with peripheral nerves and muscles

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**Object.** The purpose of this study was to describe a novel technology for implantable neuromuscular stimulation to treat complications of paralysis and disuse atrophy, including shoulder subluxation, hand contractures, drop foot, and osteoarthritis. The authors review the results so far of several pilot clinical studies of these muscle stimulation devices.

**Methods.** Miniature wireless stimulators received power and individually addressed command signals from an external radiofrequency transmission coil. One or more implants were injected through a 12-gauge hypodermic insertion tool into muscles or adjacent to motor nerves, where they provided the means to activate the muscles in any desired pattern of intensity and frequency. Randomized controlled studies in small numbers of patients are underway to identify efficacy, acceptability, best methods of practice, and any design changes that may be required to improve the technology.

Fifty patients have been enrolled in five studies; 35 patients have undergone implantation of a total of 79 BION1 devices. Comparisons with surface stimulation in patients who have suffered a stroke with shoulder subluxation and hand contractures show similar improvements in objective measures of efficacy but higher comfort levels for stimulation by implants.

**Conclusions.** Injected microstimulators represent a promising new class of technology for the rehabilitation of patients with upper motor neuropathies. As the technology evolves, practitioners may be able to use it to facilitate functional reanimation of paralyzed limbs.

**KEY WORDS** • stroke • spinal cord injury • shoulder subluxation • contracture • muscle stimulation • functional electrical stimulation

**W**E describe a new class of injectable, wireless stimulators that can be used for precise, long-term electrical activation of nerves and muscles. We review the results thus far of several pilot clinical studies conducted to investigate use of these devices to treat complications of paralysis and disuse atrophy, including shoulder subluxation, hand contractures, drop foot, and osteoarthritis. Comparisons with surface stimulation in studies still underway indicate similar improvements in objective measures of efficacy but higher comfort levels for stimulation by implants. Injected microstimulators represent a promising new class of technology for the rehabilitation of patients with upper motor neuropathies. As the technology evolves, practitioners may be able to use it to facilitate functional reanimation of paralyzed limbs.

### Clinical Need

Many neurological and orthopedic disorders reduce or eliminate voluntary recruitment of muscles. Such loss de-

*Abbreviations used in this paper:* BION = bionic neuron; FES = functional electrical stimulation; ROM = range of motion; USC = University of Southern California.

grades the ability to perform motor tasks or to maintain muscles, connective tissues, and metabolic systems that depend on muscle activity for their function and integrity. Clinicians have long understood the usefulness of electrical stimulation to activate paralyzed and paretic muscles,<sup>4</sup> but electrical muscle stimulation has not gained widespread acceptance as a standard clinical therapy. The poor acceptance seems linked to limitations in the previously available technologies, which are described as follows. 1) Transcutaneous stimulators using surface electrodes on the skin are difficult to position. It is also difficult to adjust these devices to achieve selective and reproducible effects on muscles. At stimulation intensities sufficient to activate muscles, they typically stimulate skin afferents as well. Recruitment of skin afferents may give rise to unpleasant sensations. Furthermore, surface electrodes may produce cutaneous irritation and may be considered cosmetically unappealing. 2) Percutaneous wire electrodes are mechanically vulnerable, may fail mechanically from repeated flexion, and may provide a conduit and nidus for chronic infection. 3) Surgically implanted multichannel stimulators are expensive and invasive. Thus, they are impractical for many applications, particularly in prevention and rehabilitation. Implanted stimu-

lators tend to be designed for very specific sites and uses. Consequently, a particular system can be difficult to customize to the special needs of the patient or to extend or modify function after implantation.

### Technology

In this report, we describe a new “platform” technology that was designed to have broad applicability, as described later. It consists of wireless micromodules, each of which receives power and command signals by inductive coupling from an external antenna.<sup>8,34,36</sup> One or more of these BIONs can be injected in a simple outpatient procedure similar to a Botox injection. Four generations of this technology are now in clinical trials or are being developed. All are designed to stimulate myelinated sensory or motor axons, typically in peripheral nerves or muscles. They are not used to stimulate muscle fibers directly because muscle fibers are much less excitable and generally require pulse strengths that are not achievable with this technology.<sup>30</sup>

#### *The BION1: Radiofrequency-Powered, Continuously Controllable Stimulator*

As originally proposed by Loeb, et al.,<sup>36</sup> BION1 single-channel implants receive power and digital command signals from an inductive coil that is worn over or positioned near the implants. An implant generates a stimulation pulse when it detects a match to its address. The pulse duration can be set from 2 to 512  $\mu$ sec in 2- $\mu$ sec steps, and the pulse current is regulated from 0.2 to 30 mA (17-V compliance) in two ranges of 16 steps each.<sup>8</sup> Up to 3000 commands per second can be transmitted, permitting fine control of activation in many muscles concurrently. Such implants are intended primarily for therapeutic muscle stimulation, in which patterns of electrical stimulation are used to build strength in hypotrophic muscles. Extensive preclinical testing has demonstrated that these implants form a mechanically and functionally stable and biocompatible interface when used to stimulate muscles continually.<sup>7,19,35</sup> From results obtained in accelerated in vivo testing, we infer that the implants will function indefinitely.<sup>35</sup> The clinical experience as of this writing is described in our article.

One version of this device (BION1 AMI; Fig. 1) is produced by the Alfred Mann Institute for Biomedical Engineering at USC in Los Angeles, California, and has been approved for and used in clinical investigational studies in the US, Canada, and Italy (see later discussion). Its electronic components are housed in a hermetically sealed glass capsule, which is 2 mm in diameter  $\times$  16 mm in length. Each device delivers monophasic stimulation pulses through a tantalum capacitor electrode, which is immediately recharged to the compliance voltage to maintain the charge balance required for safe long-term use in the body. The counterelectrode is made from pure iridium, which forms a conductive, nonpolarizing oxide that can be used safely to deliver the maximal stimulus pulses.<sup>44</sup> Another version of this technology with the same electronic functionality is produced by the Alfred Mann Foundation for Scientific Research in Valencia, California, for additional clinical trials not described in this article. It is housed in a ceramic package (2.5-mm diameter  $\times$  16.5-mm length) and incorporates an internal electrolytic capacitor to achieve charge balance through platinum-iridium electrodes (BION1 AMF; Fig. 1).

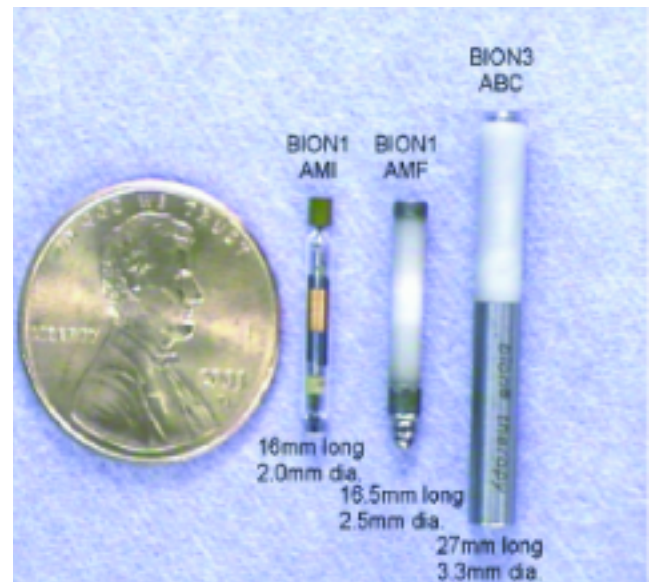


FIG. 1. Photograph depicting the BIONs now in clinical use. ABC = Advanced Bionics Corp.; AMF = Alfred Mann Foundation; AMI = Alfred Mann Institute; dia = diameter.

#### *The BION2: Radiofrequency-Powered, Continuously Controllable Stimulator and Sensor*

Work is underway to add sensing and back-telemetry systems to the BION1 platform. A new low-frequency inductive link can transmit a mix of inward command data (128 kb/second) and outward sensor data (40 kb/second) over the same 480-kHz carrier that provides power for the implants.<sup>55</sup> The sensory modalities being developed include electromyographic envelope detection (for myoelectric control), a two-axis direct-current accelerometer based on microelectromechanical systems technology,<sup>61</sup> and a form of “BIONic muscle spindle” based on range-finding readings between implants that move with the muscles in which they are placed.<sup>35</sup> Implants with both sensing and stimulation capabilities are intended for progressively more ambitious research on FES to reanimate paralyzed limbs (Fig. 2). The more advanced clinical applications such as reach and grasp function for quadriplegic patients depend on parallel development of control algorithms and fitting software that are outside the scope of this report.<sup>12-14</sup>

#### *The BION3: Rechargeable, Battery-Powered, Programmable Stimulator*

Advanced Bionics Corp. in Valencia, California, produces a commercial implant, “bion” (labeled BION3 ABC in Fig. 1), that is approved for sale in Europe and is undergoing premarket approval in the US. It incorporates a rechargeable lithium cell in a somewhat larger ceramic package (3.3-mm diameter  $\times$  27-mm length). It can be programmed to produce various preset patterns of stimulation for a few days (depending on stimulus parameters) before being recharged by an inductive link similar to that used in the radiofrequency-powered BIONs (BION1 and BION2). It is designed primarily for neuromodulation applications, in which electrical stimulation is used to modify neural activity in a dysfunctional pathway (for example, urinary urge in-

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FIG. 2. Artist's conception of radiofrequency-powered BION2 implants being used to stimulate contractions in paralyzed muscles and to sense and transmit outward information about the posture and movement of the limb to an external control unit.

continence; see later section). The battery life is projected to be 5 to 10 years depending on discharge and recharge cycles.

### *The BION4: Rechargeable, Battery-Powered, Intercommunicating Stimulator and Sensor*

As the sophistication of FES applications grows, the numbers and physical distribution of channels required for stimulation and sensing will grow beyond feasibility for low-frequency, radiofrequency-powered devices such as the BION2. Researchers at the Alfred Mann Foundation are

working on a new class of BION implants with rechargeable battery power similar to the BION3 but with a high data-rate communication protocol that allows large numbers of implants to exchange information freely among themselves and with an external controller.

## Clinical Results

Clinical and technical experience with the AMI BION1 implant as of this writing is summarized in Table 1 and described in more detail later in this article and in the cited publications. Since 1999, 80 BION1 implants have been placed in 35 patients in five small pilot studies in Canada, Italy, and the US. Although there have been no adverse events (defined as untoward signs or symptoms in patients), there have been 16 devices that did not perform properly due to various causes that have been identified and addressed by design changes. One functioning BION1 implant was removed after induction of local anesthesia because it was located near a skin fold in the groin, causing mild discomfort when the patient was seated. On several occasions, additional BIONs were injected after the initial implantation to incorporate additional muscles into the treatment or to correct for a poorly located or poorly functioning implant. Many patients have elected to continue self-administered stimulation of their BIONs long after the formal study period because they like the active muscle contraction.

### *Shoulder Subluxation in Patients With Stroke*

Flaccid paralysis of the arm occurs commonly in patients with stroke and leads to disuse atrophy of the unexercised muscles. At the shoulder, the loss of muscle contraction is often associated with subluxation of the joint because the weight of the arm stretches the fibrous capsule that normally holds the head of the humerus against the glenoid fossa.<sup>29</sup> The shoulder muscles are significantly atrophied by the time the protective reflex system is reestablished, frequently leaving the patient with a painful shoulder; such chronic pain is often difficult to manage and may interfere with rehabilitation therapy.

Surface stimulation is effective but difficult to adminis-

TABLE 1  
*Clinical experience with BION implants manufactured at AMI-USC\**

| Study                        | Location         | No. of Patients |           |               | No. of BIONs |             |           |
|------------------------------|------------------|-----------------|-----------|---------------|--------------|-------------|-----------|
|                              |                  | Enrolled        | Withdrawn | Recd Implants | Implanted    | Out of Spec | Explanted |
| acute shoulder subluxation   | Kingston, Canada | 14              | 0         | 9             | 19           | 0           | 0         |
| knee osteoarthritis          | Milan, Italy     | 5               | 0         | 5             | 10           | 0           | 1         |
| chronic shoulder subluxation | Downey, CA       | 14              | 0         | 10            | 22           | 8           | 0         |
| hand contractures            | Downey, CA       | 16              | 1         | 10            | 25           | 7           | 0         |
| foot drop                    | Edmonton, Canada | 1               | 0         | 1             | 4            | 1           | 0         |
| hand retraining              | Los Angeles, CA  | new IDE         |           |               |              |             |           |
| pressure ulcer prevention    | Downey, CA       | new IDE         |           |               |              |             |           |
| total                        |                  | 50              | 1         | 35            | 80           | 16          | 1         |

\* Clinical experience so far (10 of 14 "out-of-spec" problems arose early in the studies from an intermittently firing electrical connection in the BION1 implants that was corrected in an interim redesign of the device identified as the BION1-2). The remaining four arose from a failure of the hermetically sealed package that required a minor manufacturing change, which has been validated in accelerated in vivo testing. The BION2 implants supporting back-telemetry systems are expected to be available for clinical trials starting in 2006. Abbreviations: AMI = Alfred Mann Institute; IDE = investigational device exemption; recd = received; spec = specification.

ter long term to outpatients.<sup>20</sup> The BION1 implants injected into the middle deltoid and supraspinatus muscles allow patients to self-administer active muscle exercise at home. A typical exercise program would include two to three sessions of 20 to 30 minutes each per day, consisting of 3-second trains of stimuli separated by a 3-second off time. Low-frequency (2–5 pulses per second) stimulation at high intensities, usually three to five times the threshold for motor recruitment, was shown to be effective in preventing disuse atrophy in an animal model,<sup>17</sup> probably because it activates the calcium kinases that are responsible for trophic effects in muscle fibers. A similar exercise regimen in patients with subacute stroke, administered 4 to 10 weeks poststroke, reduced subluxation and prevented pain while minimizing overt motion and strain on the joint.<sup>18</sup>

Similar treatment is now being investigated in long-term survivors of stroke (> 6 months) who have chronic subluxation and pain. After providing informed consent, participants are randomized to either an implant stimulation group or a surface stimulation program. Both programs are followed by patients at home on a daily basis for a total of 6 weeks. After the program is complete, there is a 6-week follow-up period with no stimulation. In addition to objective measures of subluxation on x-ray films and ROM studies, each patient provided feedback on the ease of use of their respective systems. Compliance with the designated stimulation programs was monitored in both groups throughout the 6-week exercise period.

Patients who were participating actively in therapy sessions or regular exercise activities at the inception of the stimulated exercise trial continued their therapy. If a patient was not actively engaged in therapy or other forms of routine exercise, they were requested not to begin such an exercise program during the 12-week data acquisition phase of the study. Patients who were randomized to the microstimulator group were implanted with one BION each in the supraspinatus and middle deltoid muscles. After a 4- to 7-day waiting period, the BION microstimulators were activated and the patient began the 6-week exercise period. Patients receiving surface stimulation programs were provided with commercially available equipment and electrodes, shown where to place the electrodes, and began the 6-week exercise period. The study includes an optional cross-over phase in which patients who receive surface stimulation can request a second trial period to use the BIONs according to a protocol like that of the initial microstimulator group. All patients are offered the opportunity to continue either type of stimulation after the formal study period.

Changes in subluxation are shown in Table 2 for nine patients who received the implanted microstimulators and seven who exercised with surface electrical stimulation; this study is still recruiting patients. The patients receiving the implanted stimulators were slightly more compliant than those using surface stimulation (64 hours of stimulation compared with 48 hours, with target compliance set at 63 hours over the 6-week exercise program).

#### Hand Function in Patients With Stroke

The loss of motor control caused by a stroke quite commonly affects the hand. Hemiparetic patients may recover some hand function but often have residual imbalance of

TABLE 2  
Changes in subluxation\*

| Subluxation Measurement  | Value (mm)            |              |
|--------------------------|-----------------------|--------------|
|                          | BION Microstimulators | Surface Stim |
| preimplantation          | 10.9                  | 7.2          |
| after 6-wk stim protocol | 7.1                   | 7.3          |
| 6 wks poststim           | 7.6                   | 8.4          |

\* Microstimulators were implanted in nine patients, and surface stimulation was used in seven. Abbreviation: stim = stimulation.

forces from finger and wrist muscles. In the most severe cases, complete absence of voluntary extension plus spastic flexor muscle activity results in permanent flexion contractures, deforming the hand and rendering it nonfunctioning. Some patients regain voluntary flexion but lack sufficient voluntary extension to open the hand for grasping or holding objects. Much experimental attention has recently been focused on using intensive retraining therapies to take advantage of functional plasticity in areas of the motor cortex adjacent to the infarct.<sup>33</sup> In collaboration with the clinical team listed in the *Acknowledgments* section, we have started to identify suitable sites and patterns of stimulation for the wrist and finger extensors to prevent and reverse contractures, and to improve the strength and fatigue resistance of these muscles. It is our intent with these studies eventually to assess whether patients can be trained to use the muscles more effectively by triggering stimulation through electromyographic sensing of weak, voluntary contractions.

The investigation now underway is similar to the chronic shoulder subluxation study described earlier, with patients randomized between surface and implanted BION treatment; individuals receiving surface stimulation are offered a cross-over to the BION treatment after the initial 12-week study period. Two to four BIONs have been implanted at various sites to identify the most efficient and effective strategy for activating wrist and finger extensors. Table 3 presents passive ROM data from 11 patients with implanted devices and six with surface stimulation who have been studied as of this writing; this study is ongoing.

Three patients completed the 12-week stimulation protocol with surface electrodes, then chose to have BIONs implanted. These participants completed an additional 12 weeks of stimulation according to the protocol. The ROMs in these three patients when using surface and BION stimulation are compared in Table 4.

TABLE 3  
Passive ROM data in 11 patients with implants and six with surface stimulation

| ROM                 | Value (° extension)   |              |
|---------------------|-----------------------|--------------|
|                     | BION Microstimulators | Surface Stim |
| wrist               |                       |              |
| prestim             | 31                    | 22           |
| after 6 wks of stim | 42                    | 35           |
| 6 wks poststim      | 31                    | 35           |
| finger              |                       |              |
| prestim             | 27                    | 31           |
| after 6 wks of stim | 39                    | 43           |
| 6 wks poststim      | 38                    | 42           |

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Patients evaluated the ease of use of the stimulation systems at the end of the 6-week exercise period. Data obtained with this questionnaire are shown in Table 5 for both the chronic shoulder subluxation and hand contracture studies. In general, no marked differences were reported in the perceived satisfaction with the implant or surface stimulation systems except in the area of comfort; both groups of patients reported that the implanted stimulation systems were more comfortable than the surface ones. The external coils used to activate the BION implants have evolved substantially over the course of this study based on feedback from patients, caregivers, and therapists. Future patients will assess whether these improvements enhance the convenience of the implanted systems.

### Osteoarthritis of the Knee

Patients with osteoarthritis are often caught in a vicious cycle in which pain limits their ability to exercise the muscles that serve to protect the joint from further damage.<sup>6</sup> Loss of muscle strength reduces the stamina and confidence of patients when they walk or climb stairs. Typically, such individuals choose total knee arthroplasty to improve their locomotor capabilities, but this procedure is highly invasive and expensive. Furthermore, the longevity of such implants, particularly in young and physically active recipients, remains to be demonstrated.

In a clinical study conducted at the Instituto Gaetano Pini with Drs. Carlo and Delia Romano, BIONs have been implanted in two locations, alongside the femoral nerve close to the groin and in the vastus medialis muscle. Stimulation of devices implanted in the vastus medialis caused relatively localized contractions, whereas stimulation of the femoral nerve caused contractions throughout the quadriceps complex with minimal objectionable cutaneous sensation. Low-frequency stimulation at high intensities produced unfused twitches in all of the quadriceps motor units without producing sufficient tension to stress the damaged knee.

Prevention of disuse atrophy in the large, fast motor units that are most important in protecting the knee from stress requires relatively little stimulated activation, but this cannot be achieved voluntarily without generating maximal force contractions. The five patients in whom devices were implanted found stimulation with BIONs to be easy to self-administer and pleasant to use. They reported significantly decreased pain and disability; one patient who had been

TABLE 4  
Comparison of ROMs in three patients who used surface and then BION stimulation

| ROM                 | Value (° extension)     |           |
|---------------------|-------------------------|-----------|
|                     | Initial Surface Results | BION Stim |
| wrist               |                         |           |
| prestim             | 12                      | 32        |
| after 6 wks of stim | 28                      | 52        |
| 6 wks poststim      | 32                      | 43        |
| finger              |                         |           |
| prestim             | 28                      | 35        |
| after 6 wks of stim | 40                      | 50        |
| 6 wks poststim      | 35                      | 48        |

TABLE 5  
Data from the questionnaire

| Category                   | Wrist & Finger Study (%) |              | Shoulder Subluxation Study (%) |              |
|----------------------------|--------------------------|--------------|--------------------------------|--------------|
|                            | Micro-stimulator         | Surface Stim | Micro-stimulator               | Surface Stim |
| overall satisfaction       | 99                       | 100          | 88                             | 100          |
| convenience                | 96                       | 96           | 88                             | 88           |
| equipment                  | 80                       | 85           | 75                             | 75           |
| comfort                    | 85                       | 45           | 70                             | 50           |
| compatibility w/ lifestyle | 90                       | 80           | 75                             | 75           |
| improvement                | 85                       | 90           | 70                             | 70           |

scheduled for arthroplasty has postponed surgery for more than 3 years as of this writing.<sup>18</sup>

### Foot Drop

Stroke survivors and individuals with incomplete spinal cord injuries often regain substantial knee control but tend to be left with residual inability to dorsiflex the ankle voluntarily. They tend to have a slow and inefficient gait, and they are in danger from falls and compensatory heightened stress on other joints. Ankle-foot orthoses that function to lift the foot are effective but sometimes uncomfortable and limiting to wear. Surface stimulation of the peroneal nerve is difficult to apply reproducibly and to control to produce dorsiflexion without eversion or inversion.<sup>37</sup> For patients with some sensory preservation, surface stimulation often produces annoying cutaneous sensations. In collaboration with the University of Alberta in Edmonton, BION implants of the ankle dorsiflexor compartment have been combined with the WalkAide technology for triggering stimulation based on the tilt of the shank.<sup>60</sup> The entire system can be worn just below the knee. In preliminary results in one individual with spinal cord injury, BIONs were used to produce much straighter ankle dorsiflexion and similar enhancements to gait as the surface stimulation system, without producing cutaneous sensations.<sup>59</sup>

### Urinary Urge Incontinence

Many women suffer from bladder spasticity that requires them to empty their bladders frequently, even when only a few milliliters of urine have accumulated. Activity in cutaneous afferents from the clitoral nerve is known to produce inhibitory spinal reflexes on the detrusor muscle's motor neurons. This provides the basis for the Interstim (Medtronic Corp., Minneapolis, MN) surgically implanted stimulator, in which implanted electrodes are placed in the sacral foramen to activate the dorsal roots carrying the clitoral nerve afferents. Because of the mixed and variable combination of afferents at this level, many patients do not obtain satisfactory relief from this approach.<sup>9</sup> The BION3 device is small enough to be injected adjacent to the pudendal nerve as it emerges from the ischial groove, a conventional approach for obstetrical local anesthesia. The battery-powered BION3 makes it possible to program stimulation continuously without the need for a transmission coil, which is used only to turn off the stimulator when the patient desires to void.<sup>24</sup>

## Clinical Applications Under Development

### *Obstructive Sleep Apnea and Snoring*

Many adults suffer from poor airway patency while sleeping, particularly if they have accumulations of adipose tissue in the oropharynx. In some cases, this gives rise to snoring because air flowing through constricted and flaccid tissues causes vibration, which can be disruptive to spousal relationships. In other cases, the airway is completely occluded, resulting in apnea that stresses the heart and brain and disrupts rapid eye movement sleep, leading to daytime drowsiness. Various surgical reductions of the tongue and other oropharyngeal tissues have been used, but these are unpleasant and the condition tends to recur.<sup>40,53</sup> Dental appliances used to ameliorate this condition are uncomfortable or ineffective in many cases.<sup>28</sup> Continuous positive airway pressure by means of a mask and ventilator is effective for obstructive sleep apnea but physically intrusive and poorly tolerated by many patients and their sleeping partners. A surgically implanted stimulator with a nerve cuff electrode on the hypoglossal nerve and a substernal inspiratory pressure sensor produced inconsistent results because of the complex neuromuscular architecture of the tongue and because of the complexity of the device and its implantation procedure.<sup>19</sup>

The BION1 implants are presently being investigated for their ability to elicit movements of the tongue and other oropharyngeal muscles to open the airway mechanically. Because the BION1 is physically small and is not likely to wear out, it appears to be suitable for injection into small and/or surgically inaccessible muscles. One promising approach based on the neuromuscular anatomy of the tongue<sup>39</sup> is to inject a BION1 into the midline of the posterior tongue via a submandibular approach. Low threshold points corresponding to the neuromuscular endplates were found first in the geniohyoid and then in the genioglossus muscles of anesthetized pigs. Preclinical experiments with passive BION1 implants in the tongues of these pigs for 2 or 4 weeks suggest that they are well tolerated in that site. Synchronization with respiration may not be necessary because the natural dynamics of inspiratory effort and airflow tend to synchronize the patient to intermittent stimulation at the mean respiratory rhythm.<sup>42,54</sup> If the sleeping patient happens to begin inspiration when the stimulation is off, he or she naturally prolongs inspiratory efforts until the stimulation starts a few seconds later. In human experiments currently underway, percutaneous wire electrodes have been injected into the midline of the tongue via the proposed submandibular approach and used to deliver stimulation during overnight sleep studies. The stimulation was well tolerated in the first two patients, but the optimal location and stimulation patterns remain to be determined before permanently implanting a BION1.

### *Pressure Ulcers and Venous Stasis*

Individuals with spinal cord injuries and those confined to bed or wheelchair for prolonged periods tend to experience debilitating sequelae from the lack of normal physical activity. Continuous pressure on load-bearing portions of skin such as under the pelvic ischium can produce hypoxia and necrosis of the skin and underlying atrophic muscle, often requiring expensive revision surgery and prolonged and

expensive hospitalization.<sup>5,15</sup> Repeated breakdown at the same site is common. Once a vulnerable area has been stressed, prevention of further pressure problems is difficult to achieve and often requires physically complex appliances such as alternating-pressure pneumatic or hydraulic cushions. Dependent posture and the absence of blood pumping from active muscle contraction can result in venous stasis, postural hypotension, deep vein thrombosis, and eventual pulmonary emboli, particularly from the calf muscles.<sup>21</sup> These problems become particularly significant as individuals with this disability age. Prevention requires careful adjustment of anticoagulant medications and frequent physical therapy. The BION implants appear to be suitable for restoration of natural patterns of alternating muscle contraction and relaxation that normally prevent these problems from occurring in healthy individuals.

Biomechanical models and preclinical studies with transcutaneous electrical stimulation in healthy volunteers indicate that stimulation of the gluteus maximus alone (via the inferior gluteal nerve) will not achieve substantial unloading of the ischial pressure (H Kaplan, Y-H Kim, and GE Loeb, unpublished data). A clinical study of BION implants for individuals with spinal cord injury who undergo gluteal flap rotations to repair deep ischial ulcers has been approved but not yet started. The BION devices will be implanted along both the inferior gluteal nerve and the nearby sciatic nerve, which innervates the hamstring muscles responsible also for powerful hip extension. The study is designed to identify possible beneficial effects, including the following: 1) simple contraction of the muscle to redistribute pressures in and improve perfusion of the muscle and overlying skin; 2) increase in muscle volume due to trophic effects of continual stimulation; and 3) relief of skin pressure by elevating the ischium.

### *Orthopedic Rehabilitation*

Surgical repair of acute or chronic damage to muscles, tendons, and joints is often accompanied by a prolonged period of reduced function and rehabilitation, even when the repair is technically successful.<sup>32,49</sup> This is because the injury itself and the convalescent period usually require substantial reductions in normal physical activity and consequent disuse atrophy and weakening of the muscles and connective tissues. For example, patients undergoing total hip arthroplasty often fail to regain normal gait because their hip abductor muscles became severely atrophied during the preoperative progression of their degenerative arthritis.<sup>56</sup> Individuals with localized injuries of specific muscle heads, tendons, or ligaments must usually forgo active use of even the intact muscles during 6 to 8 weeks of convalescence because they lack the ability to activate those muscles selectively without straining the injured or repaired sites. The BION devices can be implanted into individual neuromuscular compartments and programmed to produce any desired pattern of activity before and during the convalescent period. Because they are inert and stable in the body, there is no need to remove them when stimulation treatment is no longer required.

### *Cerebral Palsy*

Perinatal damage to the central nervous system leads to a wide range of motor developmental problems. Many of

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these result from chronic inappropriate patterns of reflexive and voluntary muscle contraction that eventually produce permanent deformation of the muscles, ligaments, bones, and joints. Neuromuscular electrical stimulation has been investigated but may not be well tolerated, particularly in young patients.<sup>45</sup> Because of their modular nature and ability to stimulate individual muscles without producing annoying cutaneous sensations, BIONs seem well suited for use in neuromuscular stimulation to restore more normal mechanical and reflexive states.

In preclinical studies of the biocompatibility of BIONs, we noted that research animals would usually sleep during continual stimulation sessions, undisturbed by the oscillatory contractions of the stimulated muscles. Thus, it seems likely that electrically stimulated muscles could be used during sleep as "active braces" to pull out normally spastic muscles and prevent formation of contractures such as equinovarus foot deformities. Continual electrical stimulation may also lead to useful reductions in spasticity, as has been noted in patients with spinal cord injury undergoing intensive FES training to try to achieve standing and locomotion.<sup>27,31,48,57,58</sup> The precise mechanisms are unclear, but probably relate to central propagation of electrically evoked neural activity, either orthodromically in large sensory axons from proprioceptors that run with the muscle nerves or antidromically in motor axons, activating their recurrent collateral branches to the Renshaw inhibitory interneurons of the spinal cord.

### *Gastrointestinal Motility*

Many patients suffer from disorders of gastrointestinal motility, either as a result of idiopathic functional disorders or traumatic and degenerative loss of central autonomic control. Patients with insulin-dependent diabetes often suffer from gastroparesis associated with degeneration of vagal efferents, resulting in unpredictable absorption of food and unstable responses to insulin therapy. Patients with injuries and diseases of the long spinal tracts often spend inordinate amounts of time attempting to empty their bowels to prevent constipation and impaction. Gastric stimulation may also be effective for the control of morbid obesity. The gastrointestinal tract is served by sophisticated endogenous neural networks for peristaltic and other rhythmic movements. These operate by electrical and chemical mechanisms that are poorly understood and difficult to modify pharmacologically without inducing widespread side effects. It seems likely that electrical stimulation can be applied to trigger or pace local endogenous activity, thereby achieving external control over these autonomic functions.<sup>1,22,23,25,47,51</sup> The BION implants could be placed laparoscopically and would not be in danger of being dislodged by the tethering action of conventional electrode leads.

### **Potential for Functional Reanimation**

Restoring useful voluntary movement of paralyzed limbs by FES has long been the goal of researchers in this field. The focus has often been on achieving locomotion in patients with paraplegia, but this goal has been elusive.<sup>2</sup> More recently, efforts have focused on the simpler goals of standing in paraplegic individuals<sup>3,10,11,16,38,43</sup> and augmentation of grasp in patients with quadriplegia.<sup>46,50</sup> Even these simpler

goals pose challenges far beyond stimulating muscles to contract.

Clinicians who have treated patients with severe sensory neuropathies know that purposeful, stable movement depends heavily on many sources of sensory information and the integration of this information with voluntary command information to provide continuous regulation of the motor output. The simplest FES applications can use residual voluntary movement to trigger preprogrammed sequences of stimulation, such as for raising the drop foot or opening or closing the hand (see earlier descriptions). As the deficit becomes more severe, the amount of limb motion subject to voluntary control decreases and it becomes necessary to increase the number of channels of electrically stimulated muscle to be controlled. The posture of the limb must be stabilized near the middle of the ROM of joints rather than allowed to reach mechanical stop points. These requirements are motivating the development of the BION2 and BION4 technologies, which provide various sensors to detect motion in the FES-treated limb.<sup>52</sup>

Two different strategies to obtain command information have been considered. Sensors of electrical activity and/or motion in muscles and joints still under voluntary control could provide information about the intended targets of arm and hand movements.<sup>41</sup> For patients with higher lesions and more complete limb paralysis, it may be necessary and perhaps feasible to record neural activity from the parts of the motor cortex that originally controlled the paralyzed limb.<sup>26</sup>

### **Conclusions**

Various types of BION technology are being tested for their suitability to treat a wide range of clinical disorders. Their commercial availability as approved clinical products depends on demonstrations of safety and efficacy that are still in the early phases. The goal is to make sophisticated, implantable electrical stimulators available as relatively inexpensive modules that can be injected by primary care clinicians and used as needed in the course of rehabilitation.

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