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# 3 BION™ Implants for Therapeutic and Functional Electrical Stimulation

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## 3.1 OVERVIEW

Since the experiments of Luigi Galvani two centuries ago, it has been known that electrical currents can be used to stimulate muscle contraction. Achieving functionally useful movements of a multiarticular limb has been more elusive. It is only within the past 30 years that robotics engineers and neurophysiologists have fully recognized and started to address the demands that such movements place on sensors,

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actuators, and control systems. It now appears feasible to graft robotic and electrophysiological instrumentation onto a biological system to repair it, but this will require many channels of information transmission in each direction. These channels must be installed and function safely and reliably in one of the most challenging environments conceivable — the human body.

For this discussion, we shall consider three classes of treatment, based on the nature of the interaction between the patient and the technology:

- TES (Therapeutic Electrical Stimulation) — electrically induced exercise in which the beneficial effect occurs primarily offline as a result of trophic effects on muscles and perhaps the central nervous system (CNS);
- NMS (Neuromodulatory Stimulation) — preprogrammed stimulation that directly triggers or modulates a function without ongoing control or feedback;
- FES (Functional Electrical Stimulation) — precisely controlled muscle contractions that produce specific movements required by the patient to perform a task.

This chapter describes the philosophy, strategies, and technologies of a multidisciplinary and multi-institutional project that has been underway since 1988 to build bidirectional interfaces between biological limbs and electronic controllers. Three classes of BION implants have been identified and are in various stages of development.

- BION1 provides stimulation only and operates only when powered and controlled by an external transmission coil in the vicinity of the implants. These implants have completed preclinical testing and have been approved as investigational devices for a specific clinical application; three patients have been implanted to date.
- BION2 provides stimulation and sensing via bidirectional telemetry but only when powered and controlled by an external transmission coil. The feasibility of this technology has been demonstrated and fully functional implants are now in design.
- BION3 is programmed and charged by an external coil but can generate stimulation programs autonomously while drawing energy from an internal, rechargeable battery. The enabling technology is now under development.

Collaborating organizations and key personnel have included:

- Queen's University, Kingston, Ontario; G.E. Loeb and F.J.R. Richmond (former address)
- Illinois Institute of Technology, Chicago, IL; P.R. Troyk
- A.E. Mann Foundation for Scientific Research, Santa Clarita, CA; J.H. Schulman
- Advanced Bionics Corp., Sylmar, CA
- Aztech Associates, Inc., Kingston, Ontario

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- Medical Research Council of Canada
- Canadian Neuroscience Network of Centres of Excellence
- Ontario Rehabilitation Technology Consortium
- A.E. Mann Foundation for Scientific Research

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### 3.2 OBJECTIVES OF THE PROJECT

#### 3.2.1 Ease of Deployment and Use

There have been many attempts to use noninvasive interfaces with nerves and muscles based on skin-surface electrodes (discussed elsewhere in this volume) and, more recently, magnetic fields.<sup>1-3</sup> While such approaches avoid the expense and morbidity of surgery, they impose significant daily burdens on the patient, who must carefully don and maintain the interface and manage various external leads and connections in order to achieve the desired function. This burden is particularly onerous for patients with the very sensorimotor disabilities that the interface is supposed to address. Such interfaces often entail a degree of visible intrusiveness that patients find unacceptable cosmetically. At best, these interfaces tend to be poorly selective, generating unwanted sensory and motor effects even when they are applied and functioning optimally.

Surgically implanted electrodes and stimulators can overcome the technical limitations and daily use problems of external stimulation, but the costs are high and may not be justified if clinical utility is limited or uncertain. A large part of the costs associated with implantable medical devices arises from the surgical implantation itself. For many rehabilitative applications of electronic interfaces with muscle, the prescribing and treating physician is not a surgeon. The involvement of a referring surgeon, the scheduling of an operating room and anesthesia support, and the preoperative and postoperative care attendant upon surgical procedures all pose enormous logistical and financial obstacles to the widespread deployment of such rehabilitative measures. Thus, one key objective has been the development of a technology that would combine the reliability and simplicity of use of an implanted interface with the low cost and low morbidity of a nonsurgical approach.

#### 3.2.2 Modular Design

The costs of developing and testing a Class III (long-term implant) medical device have risen enormously over the past 25 years. Although some of the expense may be due to the increasing sophistication of the embedded technologies, much of it

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reflects the burden of regulatory approval. At the same time, "third party" payers of medical expenses are increasingly reluctant to approve or reimburse novel treatments until they have been proven to produce a clear cost-benefit enhancement in a particular disorder. In order to recoup increasing costs in such an environment, medical device manufacturers concentrate on large, proven applications with a high probability of success and low regulatory, liability, and fiscal risks. Unfortunately, many of the most promising clinical applications for TES or FES have no such precedents.

One of the goals of the present project has been to produce a generic and modular implant technology that can be configured and applied to a wide range of anatomical sites and physiological functions. Generic technologies are possible because all neural signaling uses the same transmission scheme. The biophysics of action potentials are the same whether they occur in muscle fibers, motor neurons, muscle spindles, touch receptors, or special sense organs such as the eye and ear.

A related goal that is particularly important in FES is to be able to assemble and build increasingly complex systems for a single patient over time. Most of the neurological disorders that underlie neuromuscular disabilities tend to change over time as a result of progression of the underlying pathology or adaptation to prior damage. Furthermore, the lifestyles and clinical needs of patients tend to evolve as they come to grips with their disabilities and learn to take advantage of the available rehabilitative technology. Thus, it is highly desirable to be able to add or replace interface channels without resorting to major surgery or endangering the function of the previously implanted components.

### 3.2.3 LONG-TERM RELIABILITY

The roots of the implantable medical device industry lie in orthopedic and cardiovascular applications in which the majority of recipients are elderly, seriously ill, or both. Perhaps the most notable widespread application of such technology to very young and otherwise healthy individuals is the cochlear implant, now the treatment of choice for children with profound or severe congenital or neonatal hearing loss<sup>4,5</sup> (see Chapter 1). This experience has heightened awareness of the substantial difficulty of designing and building sophisticated medical devices that must survive without direct maintenance for many decades in the hostile environment of the body. The problem is likely to be particularly severe in the peripheral musculoskeletal system, where implanted devices are subject to continuous motion and direct mechanical stress as a consequence of their intended motor function.

## 3.3 DESIGNING FOR SAFETY AND EFFICACY

### 3.3.1 LEADLESS INJECTABLE PACKAGE

In most electronic systems, the largest assembly costs and most likely sources of failure tend to be in the physical connections between components. This is particularly so when those connections must function in a pool of warm salt water that is constantly moving.<sup>6</sup> These considerations led us to design a system based on individual modules with the following key properties:

- Small enough to be located directly at the site where stimulation and/or sensing is required, with self-contained electrodes;
- Form factor suitable for injection through a hypodermic needle;
- Powered by inductive coupling of energy from an externally generated magnetic field;
- Capable of receiving and transmitting data by modulated radiofrequency (RF) telemetry;
- Digitally encoded device address and stimulus parameters.

The color figure shows the package for the BION1 stimulation module, which consists of a cylindrical glass capsule with two rigidly mounted electrodes on its ends. The electronic subassembly in the capsule is dominated physically by the antenna coil, which consists of about 200 turns of 1 mil insulated copper wire wound over a cylindrical ferrite form to maximize the capture of energy from the magnetic field. It is wound so as to be self-resonant at the 2 MHz carrier frequency generated by the external primary coil, which uses Class E amplification and synchronous modulation to achieve high magnetic field strength with high electrical efficiency.<sup>7</sup> The cylindrical ferrite is actually a sandwich of two hemicylindrical ferrites glued to a custom integrated circuit (IC) mounted on an alumina ceramic printed circuit board (PCB), as shown in the center portion of Figure 3.1. This arrangement maximizes the surface area available for the IC and provides a stable platform for its wire bonds plus a discrete diode chip and soldered termination of the coil windings.

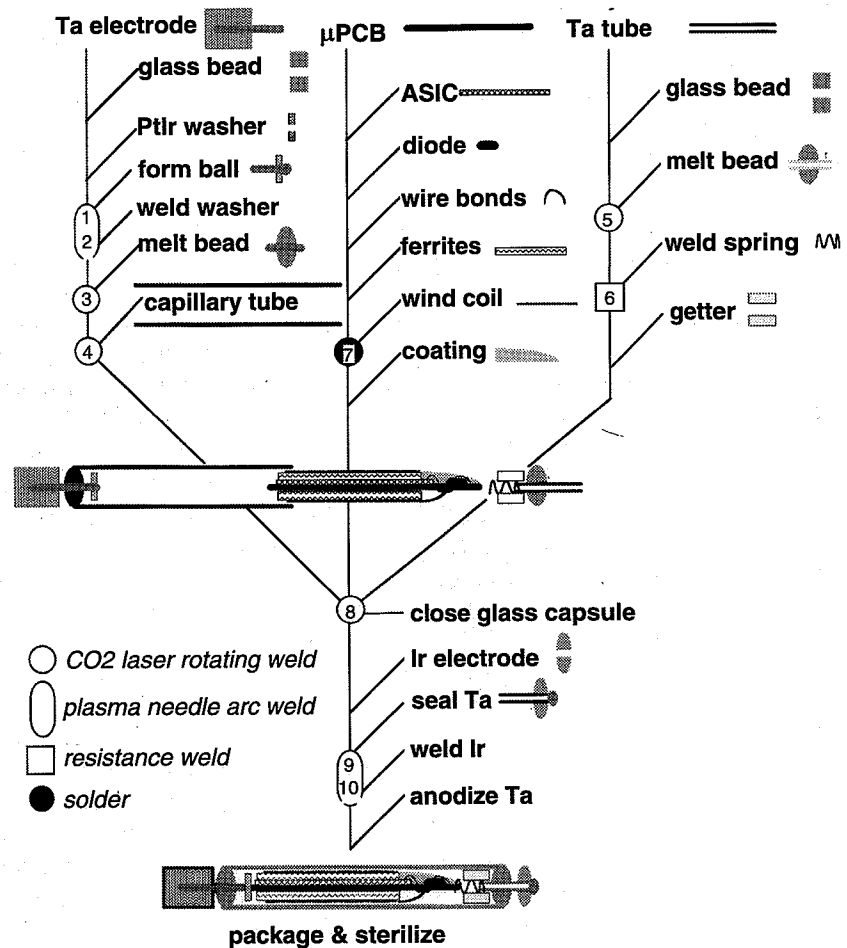
The PCBs are built in wafers of 16, using two-sided, gold-plated through-hole metallization on an alumina wafer. Before metallization, the wafer is laser-drilled in a pattern that becomes the edge-conductive detents at the ends of the PCBs after the wafer is diced. One end of the wafer makes electromechanical contact with a platinum-iridium washer welded to the tantalum stem of the tantalum electrode. The other end makes contact to a gold-plated elgiloy spring that provides an electromechanical connection to the iridium electrode at the other end, via a hollow tantalum feedthrough (Figure 3.1, right). The electronics are sealed into the capsule by sliding them into an open-ended capsule, which is formed onto the Ta electrode (Figure 3.1, left), and welding the tubular feedthrough (Figure 3.1, right) to the glass capillary walls of the capsule.

### 3.3.2 ACHIEVING AND DEMONSTRATING HERMETICITY

The most important requirement for the package is to protect the electronic circuitry from the deleterious effects of water. Sophisticated electronic circuitry such as the tuned RF power and data receiver and the digitally controlled stimulus pulse generator are particularly vulnerable to condensed moisture. Failure mechanisms include detuning of the self-resonant receiver coil, poisoning of semiconductor junctions from solubilized contaminants, and shorting of circuitry as a result of corrosion and dendrite formation between conductors with voltage differences.<sup>6</sup> At body temperature, water vapor will condense when it reaches 6% concentration (dew point) in the free space of the capsule, which is about 50% of the total inside volume of the glass capsule (0.01 cc).

BION1  
G.F. LOEB

### BION™ Glass Package Assembly Tree:



**FIGURE 3.1** The fabrication sequence of the BION1 implant consists of three major subassemblies (top, left to right): capsule subassembly built onto the Ta electrode, electronic subassembly stacked onto the ceramic micro-printed circuit board ( $\mu$ PCB), and feedthrough subassembly built onto a Ta tube. After the subassemblies are brought together, the final fabrication process includes hermeticity testing and vacuum bake-out through the still-open Ta tube followed by final closure of the Ta tube and attachment of the Ir electrode. The last process is anodization of the Ta electrode, which is accomplished by probing the Ir electrode and passing current backward through the output circuit with the Ta electrode dipped in 1% phosphoric acid. Numbers refer to ten critical joints accomplished with four different technologies as shown in the key at the lower left. The glass-to-metal (3, 5) and glass-to-glass (4, 8) seals are made by melting the glass in an infrared laser beam that provides well-controlled and very localized heating. The metal-to-metal joints (1-2, 9-10) are made in an argon plasma needle arc, which provides the intense but localized heat needed to melt Ta (2700°C) and Ir (2400°C). A resistance weld is used to attach the spring to the Ta tube without loss of temper (6) and the fine copper coil windings are terminated by microsoldering to the  $\mu$ PCB (7).

There are well-developed sealing techniques and test methods for implantable electronic devices such as pacemakers and cochlear implants, but these devices are much larger than BIONs (see nomogram in Figure 3.2). The various test methods differ in their sensitivity, which is expressed as a gas leakage rate in cc/s for one atmosphere of pressure gradient. The most sensitive method is the "helium sniffer" in which a high vacuum is applied to one side of the seal to be tested and helium gas is squirted over the other side of the seal. Trace helium gas leaking through the seals is detected by a specially tuned mass spectrometer in the vacuum line. The practical limit of this test in the laboratory is about  $2 \times 10^{-11}$  cc atm/s; the sensitivity level for production testing is usually derated to  $1 \times 10^{-9}$  cc atm/s. The equivalent leak rate for water vapor would be about  $\frac{1}{2}$  that of helium (it is related to the square root of the molecular weight of the gas). Thus it is possible to compute the length of time it would take for water vapor to reach the dew point in a capsule of a given volume if there were a leak in one of the seals at a rate just below the detection limit of the test method. For the tiny BION, hermeticity testing at even the laboratory limit could not guarantee a functional life of more than one year.

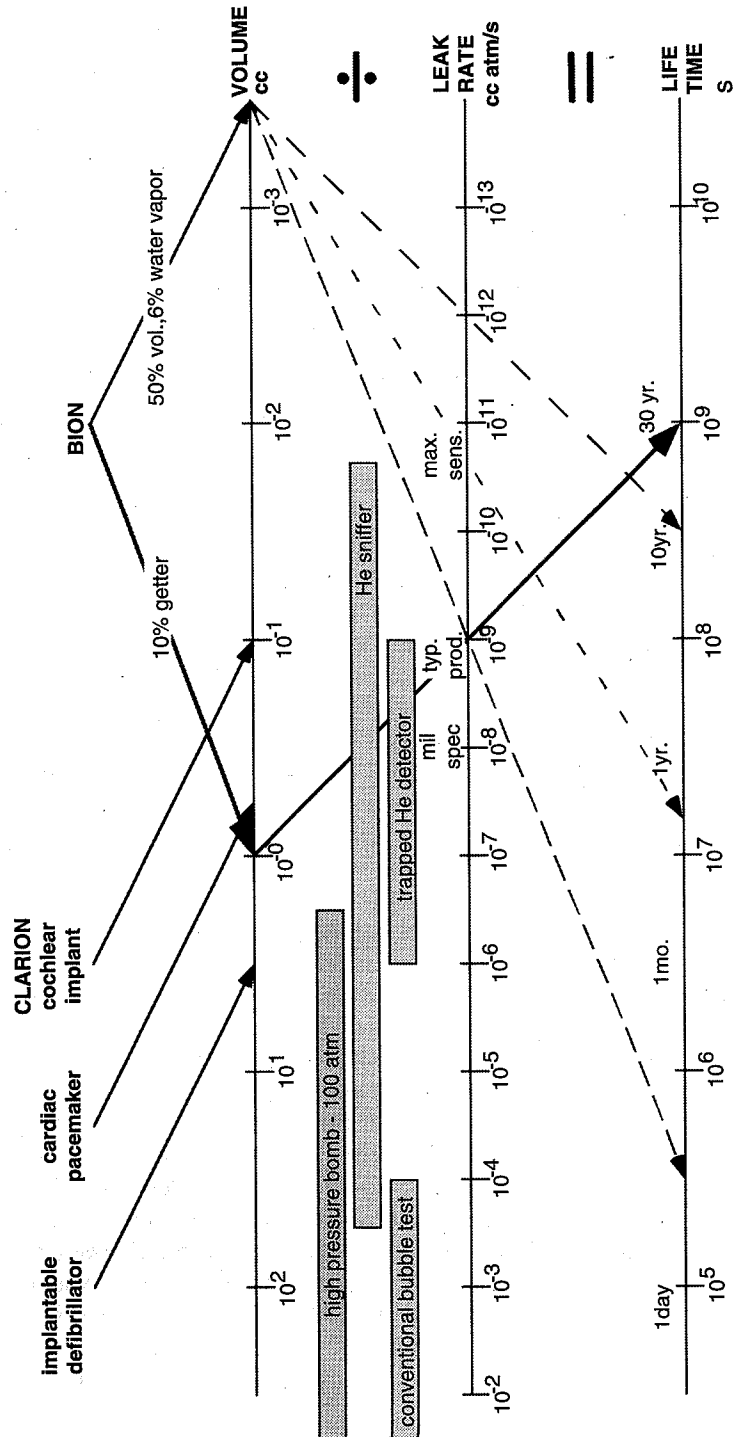
The problem of guaranteeing sufficient moisture resistance for each manufactured BION has been addressed by incorporating a "getter" that absorbs water vapor. It consists of anhydrous magnesium sulfate powder molded into a small cylinder of silicone elastomer that fits over the spring inside the BION capsule (see Chapter 3, Color Figure 1\* and Figure 3.1). Magnesium sulfate is one of a class of salts that can be used as desiccants because its crystal structure tends to bind water molecules in its interstices. Fully hydrated magnesium sulfate holds up to 8 moles of water per mole of salt. Even the small amount of magnesium sulfate in the BION getter (10% of the package volume containing  $2.3 \mu\text{g} = 2 \times 10^{-5}$  moles) can absorb a very large volume of water vapor ( $>1$  cc). In effect, the internal volume of the package for water vapor is about 100 times larger than the volume of the BION package, resulting in a projected 30-yr survival time even if the package is leaking at just below the sensitivity limit for production testing ( $10^{-9}$  cc atm/s).

Extensive qualification testing of the completed BIONs and of individual components of the seals indicates that the seals are, in fact, hermetic to a degree far beyond the sensitivity of laboratory leak-testing. BIONs built without a water getter have been soaked in saline at 160 atm pressure for over four months without evidence of detectable condensation when cooled. Other BIONs without getters have been operated for over a year with continuous output pulsing in saline while cycling between  $37^\circ\text{C}$  (3 h) and  $77^\circ\text{C}$  (9 h). In another test, BION capsules were fitted with a bare PCB in place of the usual electronic subassembly, resulting in an open circuit between the adjacent traces of metal on the PCB connected to the output electrodes. High impedance spectrograms at room temperature were compared at various intervals during one year of soaking in saline at  $85^\circ\text{C}$ , with no detectable change (this method is sensitive to a layer of condensed water vapor only 10 molecules thick).

The hermeticity of the glass-to-metal seals in the BION probably depends on chemical bonding between the borosilicate glass (Kimbel N51A) and the native oxide on the tantalum metal of the Ta electrode stem and the Ta tubular feedthrough.

\* Chapter 3, Color Figure 1 follows page 112.

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**FIGURE 3.2** Nomogram to determine the minimal guaranteed life time (s) of an implanted device from its volume (cc) divided by the minimal leak rate (cc atm/s) that can be detected during testing of its hermetic seals, as shown by log scales. Volume: Product names of various commercial implants are positioned over scale to indicate total package volume; black solid arrows indicate the volume of water vapor required to reach dew point at 37°C (6%) assuming 50% free volume. Leak Rate: Assumes 1 atm pressure head for test and use conditions. The equivalent sensitivity ranges of various conventional test methods are shown in the boxes above and parallel to the leak rate scale. Life Time: Straight lines from a given volume through a leak-rate detection limit intersect the life time scale to show the minimal reliable working life of the device; log time scale calibrated in calendar time (above) and seconds (below).



In order to prevent excess oxidation, the glass-to-metal seals are made by melting the glass using a CO<sub>2</sub> infrared laser under an argon gas curtain (Model F48-2-28W, Synrad). The hermeticity of these seals can be lost if excess residual oxygen or longitudinal grooves are left in the Ta metal from the drawing process. Earlier versions of the BION package used a tubular feedthrough of 90%Pt-10%Ir, which also produced seals that tested hermetic but tended to fail catastrophically during prolonged soaking and temperature cycling in saline because of differences in the coefficient of thermal expansion between the glass ( $5.5 \times 10^{-6}/^{\circ}\text{C}$ ) and PtIr ( $8.7 \times 10^{-6}/^{\circ}\text{C}$ ). Excess residual stress in the walls of the sealed glass capsules was measured using the photoelastic effect on the rotation of polarized light (Model 33 Polarimeter, Polarmetrics, Inc., Hillsborough, NH). By contrast, the coefficient of Ta is  $6.5 \times 10^{-6}/^{\circ}\text{C}$ . Even low amounts of residual stress, however, can result in catastrophic package failure if there are "stress-risers" in the package, such as scratches or irregularly melted regions of the glass capillary. Fortunately, these failures can be greatly accelerated by soaking in saline pressurized to 160 atm. At this pressure, the dipolar water molecules insinuate themselves rapidly into the glass defect, resulting in a propagating crack that leads to catastrophic failure of the package almost immediately.

Each seal in the BION package is tested for hermeticity and robustness at several points in the fabrication process. Each open capsule subassembly is mounted in an O-ring fixture to perform a He sniffer test of the bead-to-stem and capillary-to-bead seals. Each closed capsule is tested for hermeticity of both glass-to-glass and glass-to-Ta seals by fixturing on the open Ta tube in the He sniffer (Model ASM 110 Turbo, Alcatel). Any residual moisture in the capsule is removed by vacuum bake-out and back-filling with an inert gas mix containing 25% He. The final seal is made by melting the Ta tube closed in a plasma needle arc welder (Ultima 150, Thermal Dynamics, West Lebanon, NH) (Figure 3.1). Slow leaks in the final seal are screened by trying to detect this captured He escaping from the Ir electrode end of the package. Finally, all finished BIONs are bombed in saline at 160 atm pressure for 24 h and examined for visible cracks or condensed moisture before being cleaned and sterilized.

The mechanical integrity of the BION package and seals has also been tested in several destructive qualification tests. The glass capsule is most susceptible to breakage by three-point bending over its long axis; it will fail catastrophically if forces greater than 2 kg are applied at rigid fixation points. The maximal stresses that the BION can experience *in situ* are limited, however, by the structural strength of the soft muscle tissue in which it is intended to be implanted (about 30 N/cm<sup>2</sup> even in tetanically contracting fast-twitch muscle<sup>8</sup>). Using a combination of static and dynamic load testing and instrumentation of the capsules with strain gauges, we have demonstrated that the capsule has a safety margin of at least 4:1 once it is surrounded by at least 1 cm thick muscle. We have also been unable to induce failures of the hermetic seals when loaded axially to 1.3 kg force, which is over four times the maximal insertion force. BIONs have also been subjected to multiple episodes of random severe handling such as might occur prior to implantation, including dropping bare devices onto a steel instrument tray from a height of 20 cm and dropping packaged devices onto a tile floor from a height of 1 m, all without failure. The same devices have then survived five cycles of autoclaving and freezing without loss of function or hermeticity.

limit intersect the life time scale to show the minimal reliable working life of the device; log time scale calibrated in calendar time (above) and seconds (below).

S.F. LOEB

### 3.3.3 ELECTRODE-TISSUE INTERFACE

Electrical currents in metallic conductors such as the BION circuits and electrodes are carried by free electrons. Electrical currents in biological tissues are carried by the motion of ions. There are two basic mechanisms for passing current from the one medium to the other: capacitive "double-layer" charging and electrochemical reactions. Electrochemical reactions occur whenever the voltage across the metal-electrolyte junction reaches the free energy barrier for the reaction in question. For "noble" metals such as platinum, this tends to occur at about  $\pm 0.8$  VDC, resulting in electrolysis of water, denaturation of proteins, and gradual dissolution of the electrode into heavy metal ions.<sup>6</sup> All of these reactions are irreversible electrochemically, and they tend to generate toxic products that are severely deleterious to the adjacent tissue. Capacitive charging permits alternating currents to be passed indefinitely across the metal-electrolyte junction as long as the charge density (coulombs per square centimeter of electrode surface area) in any single phase of the waveform does not polarize the interface to this  $\pm 0.8$  VDC threshold. In conventional clinical stimulators, this is usually accomplished by using charge-regulated AC waveforms with symmetrical alternating phases and by incorporating a capacitor between the stimulus generator and the electrodes to block any residual DC leakage. Such circuitry is not practical for the BION.

In order to maximize the power efficiency and safety of the BION within the constraints of its unusually small package, we developed a novel electrode-tissue interface system based on the special properties of tantalum<sup>9</sup> and iridium.<sup>10</sup> The instantaneous power required during a single stimulus pulse at maximal intensity (30 mA through 0.5 kilohms = 0.45 W) is far higher than can be transmitted over the relatively weak inductive link between the external RF coil and the tiny implant coil. The BION takes advantage of the low duty cycle required for muscle stimulation (pulse width  $< 0.5$  ms times pulse rate  $< 20$  pps yields  $< 1\%$  duty cycle). During interpulse intervals, it stores energy from the RF field on an electrolytic capacitor. However, the BION package has little room available for such a discrete component. Furthermore, a component failure resulting in DC leakage would result in severe electrolysis if the system were powered. Instead, the BION employs a fail-safe electrolytic capacitor consisting of its output electrodes and the body fluids (Chapter 3, Color Figure 2\*).

The Ta electrode is made from a sintered powder, resulting in a porous structure with a very high surface area. It is anodized to +70 VDC (four times the maximal operating voltage of +17 VDC) in the last step of BION fabrication, resulting in an electrolytic capacitor with about 4  $\mu$ F capacitance and less than 1  $\mu$ A leakage current. The resulting tantalum pentoxide surface is biocompatible and capable of self-healing by reanodization in saline if damaged.<sup>9</sup> The counter-electrode is iridium, which develops a porous, electrically conductive oxide layer in its "activated" state.<sup>10</sup> Iridium exhibits a range of positive valence states with essentially no polarization, allowing each layer of the oxide coating to absorb and release hydroxyl ions from solution while simultaneously shifting electrons out of and into the metal, respectively. Thus,

\* Chapter 3, Color Figure 2 follows page 112.

it acts like a metal-electrolyte capacitance with an extremely large surface area and with a tendency to dissipate any net polarization by shifting the distribution of valence states among the constituent iridium atoms in the oxide layers.<sup>11</sup>

The normal operating mode of the BION is to charge continuously the output electrodes to the regulated high voltage supply powered by the RF field (+17 VDC Ta vs. Ir) and to generate stimulation pulses by discharging this capacitor through a current-regulated circuit for the desired number of clock cycles. As long as the mean rate of charge dissipation (stimulus current times pulse duration times pulse rate) is lower than the recharging capability, the electrodes stay charged to the full 17 V compliance voltage. This compliance voltage limits the maximal stimulus current that can be generated through a given load, which tends to be dominated by the resistance of the tissue in which the implant is located. This is generally in the range of 500–1000 ohms for a long term implant in muscle.<sup>12,13</sup>

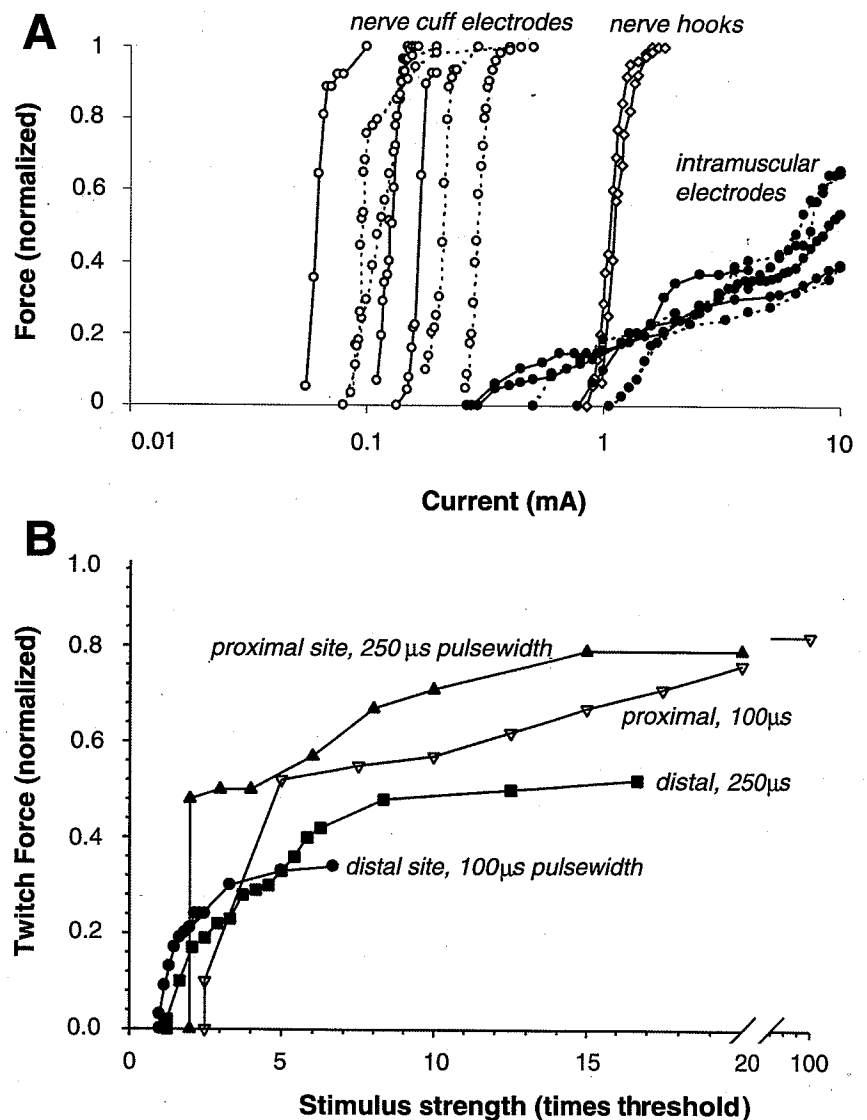
### 3.3.4 STIMULUS OUTPUT AND RECRUITMENT PROPERTIES

The present BION1 devices receive a 36-bit Manchester-encoded command that contains three 8-bit bytes of data embedded in various formatting and parity bits to avoid erroneous responses.<sup>11</sup> The first byte specifies one of 256 possible addresses. If the address matches the 8-bit value that is specified by the metallization pattern of the IC chip in a particular implant, then the remaining two bytes are decoded to specify a single output pulse emitted by that device at the end of a valid command. The second byte specifies the pulse duration of 2–512  $\mu$ s in 2  $\mu$ s steps, and the third byte specifies the pulse current of 0–30 mA in two ranges of 16 each (steps of 0.2 and 2.0 mA, respectively). Two bits of the last byte are also used to specify the constant current (0, 10, 100, 500  $\mu$ A) that recharges the capacitor electrodes between output pulses, as described above.

Intramuscular stimulation tends to produce a relatively gradual increase in the twitch contractile force of the muscle as the stimulus intensity is increased (Figure 3.3A). This is because stimulus current from the electrodes spreads throughout the volume-conductive muscle. At threshold, the first recruited motor axons are those lying nearest the Ta electrode (the effective cathode) because the current density is highest there. As stimulus intensity is increased, recruitment spreads to more distant axons. There is a general tendency for the largest axons, innervating the fast, fatigable muscle fibers, to be recruited at lower stimulation intensities than the smaller axons, innervating slower, fatigue-resistant muscle fibers. However, recruitment in muscle tends to be dominated by the relative distance between the axons and the stimulation electrodes, resulting in a more gradual recruitment of a mixture of muscle fiber types (Singh et al., in press). By contrast, when stimulation pulses are applied directly to the nerves that innervate the muscles, there is only a narrow range of stimulation strength from threshold for the first recruited largest axon to the last recruited small axon.

The actual recruitment curves for the BION in feline biceps femoris are shown in Figure 3.3B.<sup>14</sup> In this plot and in all of the software used by the clinician, stimulus strength is normalized to a single threshold intensity that is calculated as the product of pulse duration and current, which is stimulus charge. Over the range of about

BION 1.0



**FIGURE 3.3** Recruitment curves for single twitch contractions at various stimulus intensity levels, measured as force normalized to the maximal twitch for 100% recruitment of the muscle. **A.** Comparison of recruitment of cat medial gastrocnemius by nerve cuff electrodes (open circles) and nerve hook electrodes (open diamonds) on the common sciatic nerve, as opposed to intramuscular electrodes configured as in the BION (solid circles) for acutely implanted (solid lines) and chronically implanted (dashed lines) electrodes (adapted from Singh et al., in press). **B.** Recruitment of cat posterior biceps muscle by a BION1 implanted acutely in a proximal or distal location in the muscle belly, with stimulus intensity (abscissa) normalized to the threshold for a just palpable twitch at each of two pulse widths (adapted from Cameron et al., 1997). The plateau effects at less than 100% recruitment represent stimulus current levels at which compliance voltage limits were reached for an earlier version of the BION1 that had 8 VDC rather than 17 VDC compliance.

30–300  $\mu$ s, pulse duration and current are interchangeable as a way to modulate stimulus strength. Thus the ranges of these output variables available in the BION can be used to produce very fine control of recruitment. The details of recruitment depend on the location of the device in the muscle. A stimulator located near the entry point of the nerve into the muscle is able to recruit more of the axons before they fan out in their course toward more distal parts of the muscle.<sup>14</sup>

### 3.4 PRECLINICAL BIOCOMPATIBILITY TESTING

Before any new medical device can be tested in humans, it must pass a series of tests to demonstrate that the complete device and its constituent materials are unlikely to cause adverse reactions when implanted in the body. The specific tests required depend on the nature and duration of contact with the patient. The BION is a Class III device according to the U.S. Food and Drug Administration (Risk Category III in the Canadian Therapeutic Products Program), which applies to a long-term implant that delivers energy to body tissues but is not in direct contact with circulating blood. The required regulatory testing varies somewhat between jurisdictions, but conforms generally to international guidelines published in ISO standards #10993 and #14971. The more routine testing is available through various commercial contract laboratories.

#### 3.4.1 IN VITRO TESTING

Assessments of device biocompatibility generally start with tests to examine the capacity of the device to elicit cytotoxic and genotoxic effects. To evaluate cytotoxicity, we exposed L-929 mouse fibroblast cells to extracts made by soaking devices in minimal essential medium for 1–3 days. These tests showed no evidence of cell lysis or toxicity compared to negative controls. Three types of genotoxicity testing were conducted to evaluate the capacity of leachable extracts to cause damage to DNA, chromosomes, or genes. These tests included *Salmonella typhimurium* reverse mutation tests<sup>15</sup> and the chromosomal aberration tests and sister chromatid exchange assay.<sup>16</sup> No evidence of mutagenicity was seen.

#### 3.4.2 SHORT-TERM TISSUE EXPOSURE

To test the biological reactivity of BIONs, tests of acute toxicity, sensitization, and irritation were carried out in experimental animals. Acute toxicity was evaluated by injecting saline or cottonseed oil extracts from soaked devices into mice, then observing them over a 1–3 day period for evidence of toxicity compared to animals injected with control materials. Potential to produce irritation was evaluated by intracutaneous injection of saline and cottonseed oil extracts into rabbits. Injection sites of experimental and control extracts were examined daily for erythema and edema for 3 days. Sensitization was studied by injecting similar experimental and control extracts intradermally in guinea pigs. All device extracts produced reactions similar to negative controls.

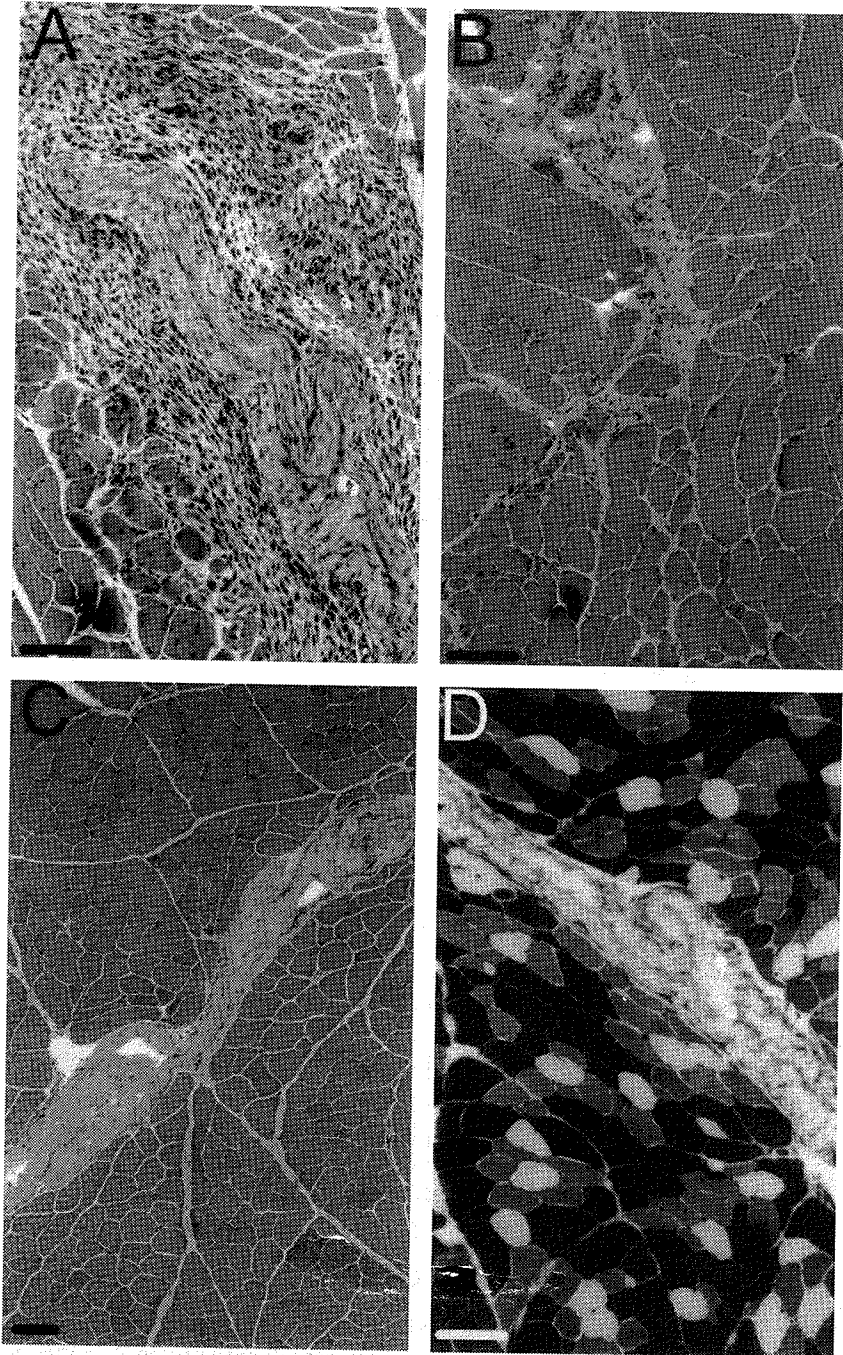
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### 3.4.3 LONG-TERM PASSIVE IMPLANTATION

A particularly salient test of biological reactivity depends on replicating the conditions under which devices will perform over a longer term in an appropriate experimental animal model. Thus, in a series of nine cats, devices were implanted in paraspinal muscles around lumbar vertebrae and in tibialis anterior muscles of the hindlimb for survival periods of one, six, and thirteen months. Different sites in the paraspinal muscles of the same animals were also implanted with negative control articles, including USP-recommended polyethylene rods, silicone rods custom-fabricated to reproduce the form of the tested devices, and BIONs whose glass package was sheathed in thin-walled silicone tubing (0.1 mm wall thickness). Each test and control article was inserted into a small pocket made in the muscle with the tips of fine scissors. The insertion sites of the devices were closed and marked with 6-0 multistranded polybutylate-coated polyester nonresorbable suture (Ethicon Ethibond). This suture also provided a test article against which the bioreactivity of the tested devices could be compared (Figures 3.4 and 3.5).

After all tested survival times, implant sites were evaluated histologically in fixed sections stained using haematoxylin and eosin, and in frozen sections reacted for adenosine triphosphatase activity (Figure 3.4). None of the implanted articles were found to change the enzyme reactivity of surrounding muscle fibers. No obvious difference could be found in the degree of inflammatory reaction around the devices and the negative control articles when the implant sites were evaluated according to their contents of inflammatory cells of different types and the extent of fibrotic and necrotic change using scales similar to those described elsewhere.<sup>17</sup> In addition, the thicknesses of capsules around the implants were measured and found to be similar around devices and control articles (Figure 3.5). In the first few months, implants were surrounded by a loosely structured connective tissue capsule about 100–500 microns thick that contained many inflammatory cells. In longer-term implants of 6–13 months, capsules were much thinner and were composed of flattened connective tissues with few associated inflammatory cells. No obvious difference was observed between reactions around the devices at six and thirteen months, suggesting that the use of a six-month survival period may be adequate to establish a stable interface between the device and the biological tissue. Interestingly, the reactions around suture material appeared to be greater than those around devices and control articles; capsules were somewhat thicker and less organized, and inflammatory cells could be identified in close approximation to strands of suture even at the longest survival times. The somewhat heightened reaction might have resulted because the braided material of the suture was more difficult to encapsulate cleanly by a muscle scar.

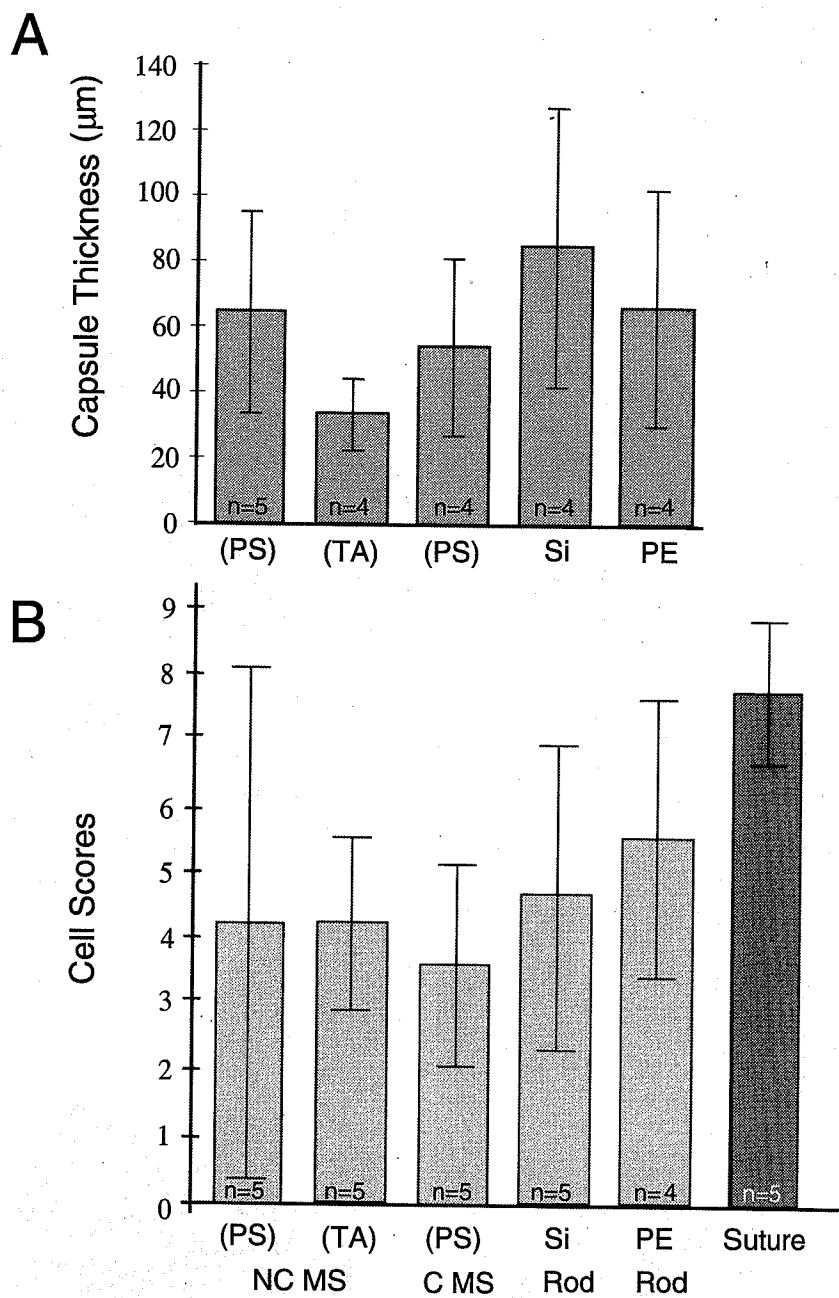
**FIGURE 3.4** Histological appearance of the connective tissue capsules around long-term implants removed from cat muscles. A. Encapsulation around silicone rod (6 month survival). Note the dense inner capsule and loose connective tissue around the implant site. B. Fibrosis in interstices between muscle fibers close to implant site (13 month survival). C. Capsule around non-coated BION (6 month survival). D. Capsule around non-coated BION (13 month survival); tissue stained with ATPase to show reactivities typical of normal muscle fibers.



bar = 100  $\mu$ m

FIGURE 3.4

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**FIGURE 3.5** Quantitative comparison of foreign body reactions around long-term implants (means with standard deviations in n cats) showing capsule thickness in A (corrected for collapse after removal of the implants) and inflammatory cell scores in B using a method modified from Black.<sup>17</sup> Implant code: NC MS = non-coated BION1 implant, C MS = BION1



Previous literature has suggested that the form factor of devices may contribute significantly to the nature and thickness of the tissue response around implanted materials.<sup>18,19</sup> In this study, however, the invaginated profiles of the devices did not seem to stimulate the production of thicker capsules than those around the smoothly contoured silicone rods. With time, the devices with invaginated surfaces around the electrodes appeared to integrate quite securely into the muscle tissue. At the histological level, streams of thickened perimysial tissue appeared to emanate from the ends of the capsules around the devices into the interstices of surrounding muscle fascicles (Figure 3.4B). We hypothesize that this web of connective tissue helps to reduce the mechanical shear between the rigid device and the surrounding muscle during muscle contractions and serves to improve the tolerance of the implanted foreign body by the muscle. In three instances, silicone or polyethylene rods were found to have migrated from their sites of implant. The thin, rather sharp ends of the polyethylene rods may have encouraged the penetration of the rod through the muscle tissue. The propensity of the glass capsules to migrate was evaluated in a separate study in cats implanted with BION-sized, smooth glass capsules. The initial implantation sites were permanently stained with a fluorescent marker that remained colocalized with the connective tissue capsules surrounding the glass capsules at the end of three months of normal physical activity.<sup>20</sup>

#### 3.4.4 CHRONIC ACTIVE TESTING

The aforementioned study was carried out using passive devices. However, when BIONs are used for their intended therapeutic purpose, they emit electrical pulses to stimulate motor axons and produce muscle contraction. To test whether the active devices would have greater foreign-body responses than passive implants, an additional series of four cats was implanted with active BIONs in four muscles of one hindlimb and passive BIONs in the other.<sup>12</sup> The active devices were used to stimulate muscles for two hours each day, five days per week for three months. The biological reactions to the implanted devices were similar for active and passive implants, according to the quantitative outcome measures used in the passive trials described above. Stimulation was carried out in fully alert, behaving cats so that their reactions to the stimulation could be observed. Typically, the cats tolerated the stimulation well. They generally ignored evoked movements of their limb and slept through much of the stimulation period. In only one animal was a negative reaction observed when stimulus currents were increased. This device had low stimulus thresholds and was retrieved from a site very close to the parent nerve, where small movements of the electrode with respect to the nerve might have great impact on the threshold of the stimulation and the recruitment of sensory fibers in the parent nerve. Such a

**FIGURE 3.5 (continued)** with a 75  $\mu\text{m}$  thick sheath of silicone rubber tubing over the glass capsule, Si Rod = medical silicone in the size and shape of the BION1, PE Rod = standard USP negative control article, suture = Ethibond™ 6-0 multistranded polybutylate-coated polyester. Site codes: (PS) = paraspinal muscle, (TA) = tibialis anterior muscle.

reaction was not seen in other animals in which devices presumably were placed at a greater distance from the parent nerve.

In two cats active devices were also placed in the muscles sartorius and semitendinosus, which are known to be composed of muscle fibers that are shorter than the muscle fascicles and are arranged in series within the fascicles. After a few weeks of stimulation, one animal began to lick the skin overlying the semitendinosus muscle in the periods between stimulation trials. This animal was sacrificed within a few days of the onset of the licking. Histopathological analysis of semitendinosus suggested a modest degree of damage to a small region of muscle tissue extending for several mm beyond the end of the device. The circumscribed region was marked by a modest increase in fibrosis of the connective tissues. Some muscle fibers appeared shrunken and had centrally placed nuclei.<sup>12</sup> We speculate that this small region of muscle damage may be similar to a common type of exercise-related injury (sometimes called a "hamstring pull injury") that has been reported in long, strap muscles of exercising humans.<sup>21</sup>

### 3.5 CLINICAL APPLICATIONS AND THEIR TECHNOLOGICAL CHALLENGES

The three classes of treatment described at the beginning of this chapter (TES, NMS, and FES) each include many specific clinical applications for which BION technology in its present or future form might be suitable. The selection of a particular application requires a major commitment of resources to the development of external hardware and software, the design and conduct of a clinical trial, and the regulatory process for investigational device approval and eventual commercialization of a product if the trial is successful. We examined twenty different applications according to a cost-benefit analysis based on such factors as the amount of research required to demonstrate efficacy, the clinical value of the treatment if successful, the size of the market, and the likelihood of reimbursement.<sup>22</sup> The following is a technical analysis of two of the more promising applications to emerge from the cost-benefit analysis.

#### 3.5.1 TES FOR SHOULDER SUBLUXATION IN STROKE

The presently available BION1 implants provide accurate and reproducible muscle stimulation, but they do not provide detection of volitional command signals or sensory feedback to permit fine control (see below). They also require a transmitting coil to be in close proximity to the implants during stimulation. The present version of the RF power and control system consumes approximately 2 W of power and is designed to be powered by an AC/DC converter plugged into a conventional receptacle rather than a portable battery. Thus the BION1 system is most suitable for TES applications in which a sedentary patient uses the system to exercise and strengthen muscles for relatively brief periods each day.

For the initial clinical testing of the new BION technology, we selected an application in which it is relatively easy to implant the devices, assess their functionality,

and achieve a clear and quantitatively measurable clinical outcome in a reasonably short period of time. This is the prevention of shoulder subluxation in stroke patients by TES-induced muscle exercise. The most common residual defect of a stroke is paralysis of the contralateral arm, with atrophy of the affected muscles. The majority of these patients go on to develop chronic pain in the affected shoulder as the weight of the arm gradually stretches the flaccid muscles and pulls the humeral head out of its socket (the glenoid fossa).<sup>23</sup> Conventional treatments with slings and painkillers is generally ineffective and tends to interfere with any rehabilitation effort. Electrical stimulation of the affected muscles via skin surface electrodes (so-called deep transcutaneous electrical neuromuscular stimulation) has been reported to prevent and reverse this problem,<sup>24</sup> but each treatment session requires a trip to the clinic to apply the electrodes and adjust the stimulation parameters.

Figure 3.6 shows the clinical system for use of BION implants to prevent shoulder subluxation. One or two BIONs are implanted into each of the two key muscles: the middle head of the deltoid and the supraspinatus. The location can be determined accurately before each BION is implanted by delivering stimulation pulses from a conventional stimulator through the modified trochar of the insertion tool. The insertion tool is based on a conventional 12 gauge Angiocath™ needle, consisting of a plastic sheath about 10 cm long over a sharp, removable trochar for penetrating skin and fascia. By adjusting the stimulation intensity as the target muscle is palpated, it is possible to identify that the tip of the insertion tool is within the target muscle and close enough to its innervation zone to permit reasonably strong recruitment. The trochar is then removed while holding the sheath in place and the BION is slipped down the sheath and extruded from the tip by pushing a blunt plunger while withdrawing the sheath.

After allowing the BIONs to settle *in situ* for a few days, the clinician determines the threshold for muscle activation at each site and develops an exercise program based on a sequence of ramped and overlapping trains of stimulation at the various sites. A software package has been written in Visual Basic 5 to provide an intuitive graphical user interface for the clinician. It automatically tracks all of the clinically relevant data in a time-stamped relational database, including the serial numbers, addresses, and locations of each implant; the electrical thresholds over time; the various exercise programs devised for the patient's use; and the compliance of the patient in using the system at home. The exercise programs are downloaded from the clinician's personal computer into a microcontroller-based portable device (called a Personal Trainer™) that the patient operates simply by hitting start and stop buttons. The elapsed usage is uploaded into the database when the patient returns to the clinic with the Personal Trainer for testing and reprogramming as needed.

Several outcome measures have been validated in preclinical testing or adopted from the clinical literature on shoulder subluxation. The most direct demonstration of efficacy is the prevention of the loss of muscle mass that normally accompanies disuse atrophy. Imaging techniques such as magnetic resonance (MR) and x-ray computed tomography (CT) have been used to measure the cross-sectional area of individual muscles,<sup>25</sup> but they are lengthy and expensive procedures to perform repeatedly. Measurement of diameter from well-positioned ultrasound scans has

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Treating shoulder subluxation in stroke patients:

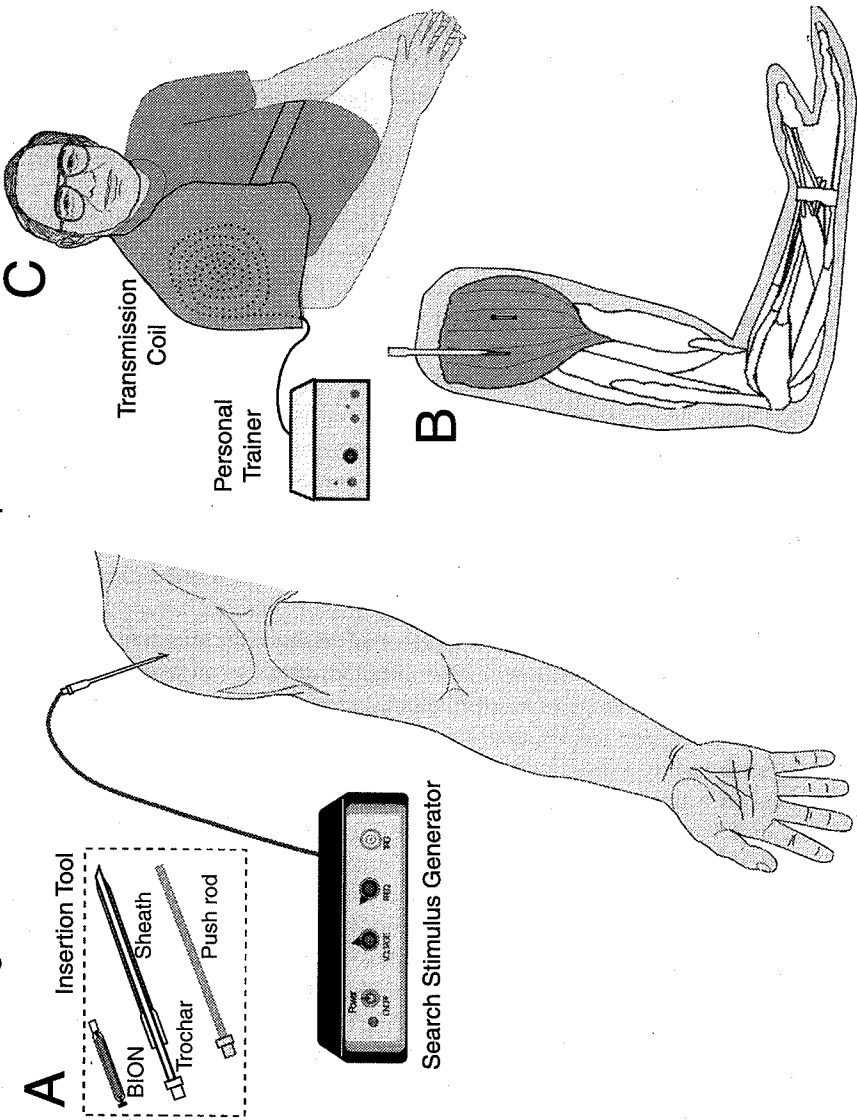


FIGURE 3.6

been validated by comparison with MR in the same normal subjects.<sup>29</sup> Such scans will be used to measure atrophy by comparison with the unaffected arm. Other important outcome measures include distance of subluxation as measured by palpation and oblique radiographs, and range of passive motion without pain, which declines rapidly as subluxation develops.

At the time of this writing, two stroke patients have been implanted with two BIONs and are receiving regular TES to build up atrophic deltoid and supraspinatus muscles. The study will eventually include 30 subjects in a randomized, prospective, controlled, cross-over paradigm.

### 3.5.2 FES FOR ASSISTED GRASP IN STROKE AND SPINAL CORD INJURY

BION2 technology will provide outgoing telemetry of data from various modalities of sensing in order to achieve FES. The sensing modalities that appear immediately feasible include bioelectrical signal recording from the existing electrodes, range-finding between implants (based on implants quantifying the strength of the outgoing RF transmission of another implant), and acceleration (based on incorporating a microelectromachined silicon [MEMS] sensor in the implant package).

The BION2 incorporates a novel power and data transmission scheme called "suspended carrier" that reduces the power requirement about 5-fold from the BION1 amplitude-modulated 2-MHz carrier. The power oscillator can be switched completely off and on again within two carrier cycles and with minimal power loss by electronically opening the tank circuit at the instant when all of the energy in the circuit is in the form of charge stored on its tuning capacitor (Troyk, Heetderks and Loeb, U.S. Patent #5,649,970, July 22, 1997). All of the outgoing telemetry and some of the low-level sensing will occur during periods of carrier suspension.

Figure 3.7 illustrates a typical scheme for using multiple BION2 implants to achieve the relatively simple clinical FES function of assisting a patient with weak voluntary grasp. This application has the advantage that all of the muscles that must be monitored and stimulated are located in the forearm, where BIONs can be easily powered and controlled by a transmission coil embedded in the sleeve of a garment. A somewhat simpler scheme has been tested clinically, using transcutaneous stimulation of digit flexors triggered by mechanical monitoring of voluntary wrist flexion.<sup>26</sup>

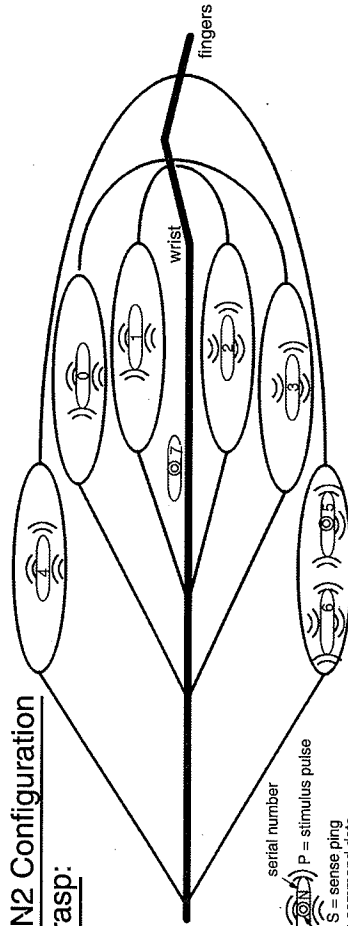
Functional grasp of objects includes several distinct postural strategies, each requiring the coordinated recruitment of many muscles.<sup>27</sup> The example chosen is a relatively crude palmar prehension task in which an object is captured by curling

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**FIGURE 3.6** A. Insertion of BION1 implants into supraspinatus (not illustrated) and middle deltoid muscle using an insertion tool that permits application of search stimuli to identify the correct site. B. Extrusion of BION1 implant into desired site in middle deltoid. C. Daily self-administered TES session requires donning of transmission coil configured similar to a heating pad and push-button operation of Personal Trainer™ into which clinician has downloaded one or more customized exercise programs.

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**Simplified BION2 Configuration  
for Assisted Grasp:**



T = data telemetry  
 Se... = sense emg) serial number  
 P = stimulus pulse  
 Q = ping S = sense ping  
 - = receive command data

RF carrier — C T

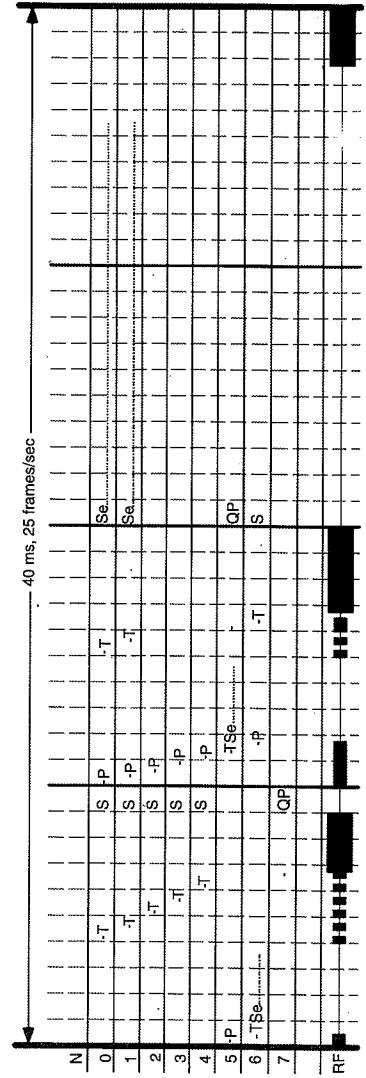


FIGURE 3.7

the fingers around the object and forcing it into the palm. Many patients with strokes and cervical spinal cord injury can initiate the first phase of such a grasp, which is to stabilize the wrist in extension so that the subsequent contraction of the long finger flexors is not dissipated by their flexion action at the wrist. In Figure 3.7, BIONS #0 and #1 in the two wrist extensors detect the onset of this voluntary activity by monitoring their electromyographical (EMG) signals. The external controller then coordinates the electrical stimulation of the other wrist and digit muscles, monitoring the resulting hand motion by measuring the distances between the various implants as the muscles change length. Changes in the shape of a contracting muscle may cause changes in the recruitment properties of an intramuscular stimulator and in the force-generating capabilities of stimulated motor units. In the example, BIONS #5 and #6 in the critical long digit flexor muscle each monitor the M-wave produced by the stimulation from the other implant as well as the distance between the two implants. The external controller can then compensate for such effects in order to maintain the desired level of grip force.

Many other FES applications can be imagined using different combinations of stimulation and sensing (see Chapters 2 and 5 for additional examples). All are likely to require some form of sensory feedback to replace the reflexive control of the spinal circuitry for normal voluntary behaviors and some form of command signal detection based on mechanical or electrical sensing of a part of the neuromuscular apparatus that remains under voluntary control. As the peripheral interfaces available through BION technology become more sophisticated, the limiting factor in performance will shift first to the control algorithms for using the sensory feedback and then to the integration of the sensory and motor components with the cognitive and volitional functions of the brain itself. These challenges are covered in other chapters in this volume.

**FIGURE 3.7** BION2 implants will be capable of various sensing modalities as well as generating stimulation pulses. As illustrated in the icon key, a given implant can be commanded to sense bioelectrical signals such as EMG for a programmable sensing interval and programmable gain. While the power RF carrier is turned off (state T), the implant telemeters out a digitized value corresponding to the area of the EMG waveform. For position sensing, a given implant can emit a standardized RF burst (ping) while other implants record and digitize the local field strength of the ping for later outgoing telemetry. The RF carrier can exist in one of two on-states: *D* for continuous modulation to encode command data addressed to individual implants and *C* for continuous unmodulated carrier, which maximizes field strength to precharge the power storage capacitors in the implants to function during subsequent carrier-off periods. Data sent to each implant include synchronization codes to permit various implants to begin sensing and sending data back upon detection of particular carrier states. The state diagram at the bottom shows the sequence of functions in each implant for one typical frame of control, with frames repeated at 25 frames/sec. Each implant can be sent a command in 160 to 270  $\mu$ s, depending on the number of new parameters required for its next function. Back-telemetry of one 8-bit data byte (plus formatting bits) from one implant requires 256  $\mu$ s.

S.F. W. B.

FIGURE 3.7

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