NEURAL ENGINEERING'S IMAGE PROBLEM

Despite a string of successes, implanted prostheses remain in the shadows By James Cavuoto

JENNIFER FRENCH, who was paralyzed from the waist down in 1998 as a result of a snowboarding accident, has a new mission. Standing up? Walking? No. Been there. Done that. With the help of electronics implanted in her legs and lower torso, she can already stand up out of her wheelchair and even move around using her walker [see photos, "Standing Up for Neurotech" and "At the Flick of a Switch"]. But now she's taken on a different sort of challenge: motivating others with neurological injuries and their caregivers to consider implanted devices. It's a tougher sell than you might think.

Neuroscientists are, at last, realizing one of the greatest ambitions in recent medical history: the ability to tap directly into the human nervous system to restore motor and sensory functions in patients who lost them because of injury, illness, or stroke. Those with certain birth defects could also benefit. The advances are being driven by a confluence of developments, including better understanding of the anatomy and function of nerve fibers and the availability of new electrodes for interfacing to those fibers. Also, and perhaps most significant, improved neuromuscular-control algorithms are permitting more natural movements in patients by applying more refined electrical signals to the nerves. All told, the advances are a small but significant step in what will surely be one of technology's most enduring quests: the medical restoration and ultimately even enhancement of human capabilities by advanced implanted prosthetic systems.

Ironically enough, however, amid these lofty, science-fiction-like dreams, the budding endeavor is grappling with a serious problem. Neural engineers, particularly those designing devices to overcome paralysis, get little respect from the authorities that dole out research funding and venture capital investment, along with the media attention that accompanies both. The reasons for this short shrift have little to do with clinical results and users' desires and rather a lot to do with public perception, the clout of the pharmaceutical industry, and a pervasive bias against implanted devices. Implant researchers at Aalborg University in Denmark, Tohoku University in Japan, the University of Ljubljana in Slovenia, and other major neurotechnology centers point to a string of impressive results with human beings. Meanwhile, the powerful, well-funded, and media-savvy pharmaceutical and biotechnology industries regularly trot out films of partially paralyzed rats recovering some movement through the miracles of stem-cell therapies, neural-regeneration techniques, or experimental pharmaceutical agents. California researchers, for example, recently felt comfortable enough with their public clout to launch a voter initiative seeking US $3 billion for stem-cell research in the state. The grapevine soon delivers the news to sufferers of paralysis, stroke, or Parkinson's dis-

STANDING UP FOR NEUROTECH: Jennifer French, who uses functional electrical stimulation to stand, says many people with spinal cord injuries are in the dark about such devices.

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ease, for example, who become hopeful of a near-term cure. The patients become less likely to go with an implanted device that is already available, because it is often regarded as a temporary fix at best, or an impediment at worst.

French herself, who recently formed a nonprofit organization called the Society to Increase Mobility (STIM), in Tampa, Fla., to help spread the word about neural engineering, knows the problem all too well. "There is a spinal cord injury community out there that believes that they should do nothing to their bodies until the cure is here," she says. "The challenge is: how do you reach those clinicians and patients in an environment that is overshadowed by the promise of a cure soon to come?"

Meanwhile, the list of people who could have more productive, more comfortable, or more active lives with these devices keeps growing. Each year there are roughly 10 000 new cases of spinal cord injury in the United States alone. Electrically stimulating nerves or muscles, a technique known as functional electrical stimulation (FES), is also applied to the fast-growing group of age-related infirmities. The methods include the use of spinal cord stimulators, which treat chronic pain or stop urinary incontinence; devices to diminish the tremors of Parkinson's disease by feeding electrical impulses to structures deep within the brain; and stimulators that send signals to the left vagus nerve in the neck, on its way to the brain, in order to quell epileptic seizures. Even though many patients are reluctant to consider a neurostimulation device, a study by publisher Neurotech Reports, San Francisco, projects that the market for implanted systems will reach $3.6 billion by 2008 and it is now growing at an annual rate of 36 percent [see "Industrial Neurotech"].

AT THE FLICK OF A SWITCH: An external controller sends commands to an implanted device that jolts Jennifer French's muscles into action in the correct sequence, allowing her to stand up out of her wheelchair.

Supporters of FES take heart in the history of neuroengineering's top success story so far, the cochlear implant. After an unencouraging start, when the device was seen as a threat to deaf culture, it has gone on to restore at least some hearing to an estimated 70 000 people worldwide, including a growing number of children. Typically, someone with an implant can converse on the telephone without the other person knowing the caller was once deaf. And these implants are getting better all the time as electrodes become smaller, sound-processing electronics get smarter, and surgical implantation procedures are simplified. Researchers are hopeful that they are on the verge of repeating this success with retinal implants. At the moment, the first dozen or so blind volunteers to receive retinal implants have only very crude vision—detecting light, movements, and coarse shapes like the letter L. But even this rudimentary vision has given hope to thousands of blind people.

ONE OF THE MORE telling examples of how good neurotechnology has fallen by the way is the story of the Freehand implanted hand-grasp stimulator for quadriplegics, which until 2002 was marketed by NeuroControl Corp., Valley View, Ohio. Originally developed at the nearby Cleveland Functional Electrical Stimulation Center, Freehand consists of an eight-channel stimulator implanted like a pacemaker in the chest wall. Each channel is connected to electrodes that are surgically attached to the nerves of the hand and wrist. The user controls the device by twitching the opposite shoulder, which activates a mechanical switch. The switch signals the stimulator to send electrical impulses to contract the muscles that make the hand grasp an object. More than 200 individuals with spinal cord injury at the fifth or sixth of the seven bones in the neck (counting from the skull) have been implanted with the device and use it to perform everyday tasks like combing their hair.

In general, the higher up the injury is on the spinal cord, the more loss of function results. Quadriplegics whose injuries are at the base of the neck (C5–C6, for the fifth and sixth cervical vertebrae, in medical lingo) have some upper body control, while those with injuries at the second neck bone (C2), such as Christopher Reeve, lose not only upper body function but the ability to breathe as well. Those with injuries at the middle or lower back retain the use of their upper extremities but usually become paralyzed from the waist down.

Unfortunately, NeuroControl management pulled Freehand from the market—not because it didn't work, or users didn't like it, or it wasn't safe, but because of basic economics. The 1000 or so new cases of C5–C6 spinal cord injury each year were not enough to justify continued marketing of the device, and not enough of the existing population of quadriplegics were electing to have the device implanted. The cost of the device and the implantation surgery, about $50 000, was another deterrent, although insurers were beginning to cover the cost at the time NeuroControl pulled the plug.

NeuroControl's investors liked the numbers better in the stroke market, with four million existing cases in the United States and 700 000 new incidents each year, and so changed focus accordingly. Stroke is more likely to be treated with therapeutic electrical stimulation than functional stimulation. Therapeutic stimulation seeks to restore the natural state of a patient's neuromuscular system by using electrical impulses applied to paralyzed or weakened muscles, usually through electrodes placed on the surface of the skin. Therapeutic stimulation can also take advantage of an inherent adaptability in the brain to be retrained and recover some of the lost function. But because the connection between the brain and the body is damaged in people with spinal cord injury, therapeutic stimulation does not have the same degree of effect.

Joe Katzenstein, vice president of sales and marketing at NeuroControl, pointed out a more subtle factor that limited Freehand's penetration into the existing population of quadriplegics. Freehand users—and the orthopedic surgeons who implanted them—were generally pleased with the device's performance. But doctors in the branch of medicine responsible for spinal cord injury patients, physiatry, were slow to recommend the product to their patients. In part this stems from an inherent distrust of implanted

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INDUSTRIAL NEUROTECH

The neurostimulation market will reach US $3.6 billion by 2008, says publisher Neurotech Reports. Here are the companies to watch and what they do.

1 MEDTRONIC INC.
Minneapolis, Minn.

Deep brain stimulators, spinal cord stimulators, sacral nerve stimulators

- Market leader in neurostimulation
- Activa deep brain stimulator recently approved for Parkinson's and other tremors
- Spinal cord stimulators treat chronic back pain
- Sacral nerve stimulators for urinary incontinence

2 COCHLEAR LTD.
Lane Cove, Australia

Cochlear implants, neural prostheses

- Market leader in cochlear implants
- Its Neopraxis Pty. group is developing a standing/walking prosthesis for the paralyzed

3 SYNAPSE BIOMEDICAL LTD.
Oberlin, Ohio

Diaphragm pacing system

- Phrenic nerve stimulator for pacing breathing eliminates need for mechanical ventilator in severely paralyzed

4 ADVANCED BIONICS INC.
Sylmar, Calif.

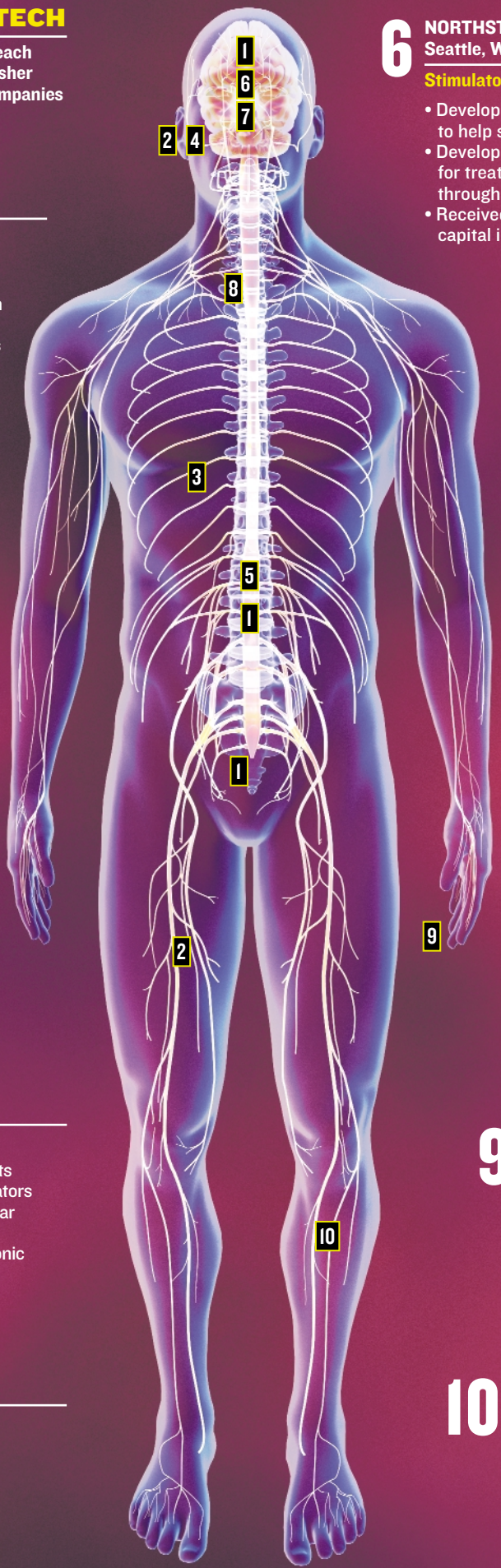
Cochlear implants

- Among top three in cochlear implants
- Hopes to sell injectable Bion stimulators for urinary incontinence within a year
- Coming: spinal cord and deep brain stimulators to compete with Medtronic

5 ADVANCED NEUROMODULATION SYSTEMS INC.
Plano, Texas

Spinal cord stimulators

- No. 2 in neurostimulation
- Genesis spinal cord stimulator has cut into Medtronic's market
- Coming: deep brain stimulator



6 NORTHSTAR NEUROSCIENCE
Seattle, Wash.

Stimulators for stroke rehabilitation

- Developing brain stimulator to help stroke patients recover movement
- Developed, then sold off a stimulator for treating back pain using through-the-skin electrodes
- Received $37 million in venture capital in 2002

7 CYBERKINETICS INC.
Foxborough, Mass.

Brain-computer interfaces, microelectrode arrays

- Start-up is developing BrainGate brain-computer interface to interpret signals from brain, so paralyzed patients can control neural prosthesis or external device
- Recently merged with Bionic Technologies, maker of an implantable microelectrode array

8 CYBERONICS INC.
Houston, Texas

Vagus nerve stimulators

- Device implanted in chest wall activates vagus nerve leading to brain that is thought to pace physiological functions like respiration and heartbeat
- Stimulator has been shown to suppress epileptic seizures, and is being evaluated for treating depression and obesity

9 AFFERENT CORP.
Providence, R.I.

Sensory stimulators

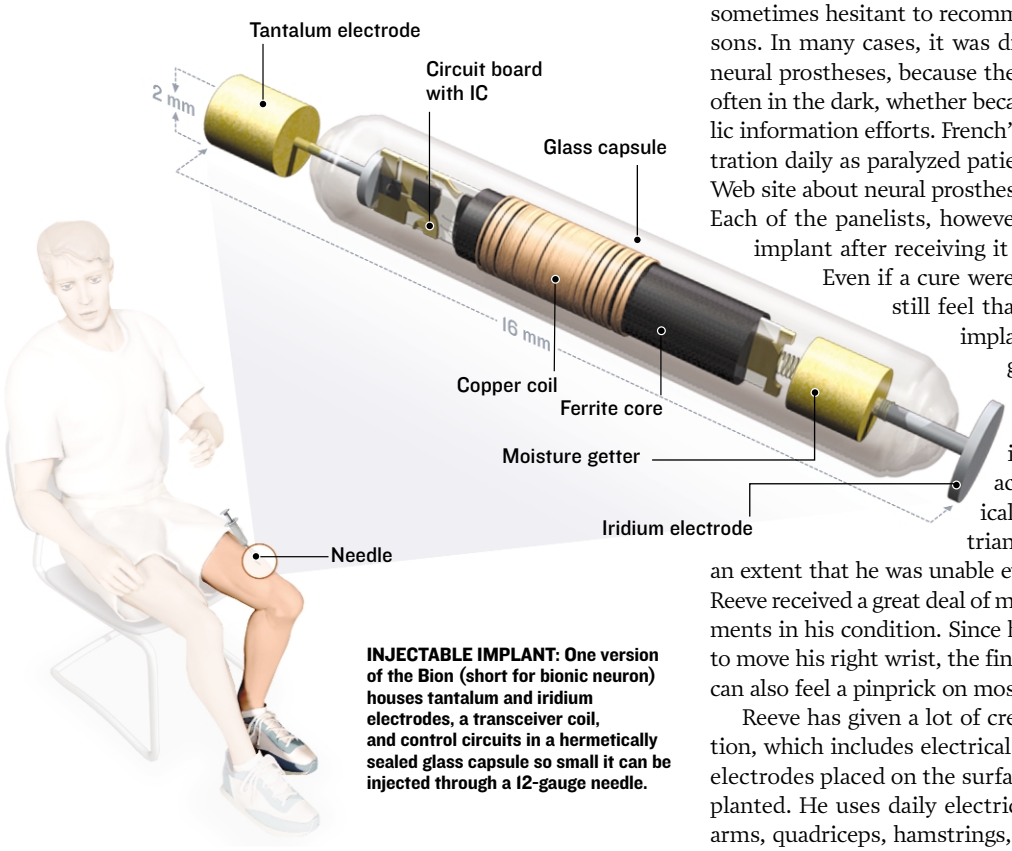
- Device for restoring sense of touch and balance lost because of stroke, diabetes, or other disorders

10 ROBOMEDICA INC.
Culver City, Calif.

Step training

- System to teach people with neurological disorders and other impairments to walk

HYBRID MEDICAL ANIMATION



INJECTABLE IMPLANT: One version of the Bion (short for bionic neuron) houses tantalum and iridium electrodes, a transceiver coil, and control circuits in a hermetically sealed glass capsule so small it can be injected through a 12-gauge needle.

devices—some physiatrists fear patients will be used to test potentially dangerous devices.

While calling the Freehand effort "a good start," Steven Kirshblum, a leading physiatrist and director of the spinal cord injury program at Kessler Institute for Rehabilitation in West Orange, N.J., thinks that a leadless stimulator that does not require as much surgery to implant would gain more acceptance.

Another factor was the lack of awareness of the product and its capabilities among both physiatrists and their patients. Katzenstein acknowledged that NeuroControl could have done a better job of promoting the product to physiatrists in the early stages of clinical trials. But Kirshblum believes that health care professionals beyond his small group must be educated about FES. People with spinal cord injury tend to follow the advice of their local physicians, he notes.

The industry in general faces hurdles in public awareness and clinician readiness, according to panelists at a 2001 neural engineering workshop at the U.S. National Institutes of Health (NIH), where a panel of implanted-device users shared their experiences. The panel included a deaf person who had received a cochlear implant, a person with Parkinson's disease who had received a deep-brain stimulator to subdue her tremors, a quadriplegic who had received the Freehand hand-grasp stimulator, and a paraplegic who had been implanted with an experimental standing prosthesis.

Each of the four reported a similar feeling prior to deciding to go ahead with the implant: a concern that a cure for the particular disease or disorder was imminent and that an implant might somehow interfere with that cure. Such interference is unlikely, but implant makers have been lax in dispelling this fear. For instance, in the early days of cochlear implants, still the only real solution for most deafness, the devices were used only on one side so that patients would have a "pristine" ear available for a future miracle cure.

The NIH panelists also felt, at the beginning, that electrical stimulation represented only a stopgap technology, not a permanent solution to their disorders. And they reported that clinicians were sometimes hesitant to recommend the procedure for financial reasons. In many cases, it was difficult even to find information on neural prostheses, because the relevant patient communities were often in the dark, whether because of clinician apathy or weak public information efforts. French's organization, STIM, sees this frustration daily as paralyzed patients download information from her Web site about neural prostheses that just isn't available elsewhere. Each of the panelists, however, was extremely satisfied with the implant after receiving it and regretted not opting in sooner. Even if a cure were to be found tomorrow, each would still feel that it was worth the effort to get the implant, recover from surgery, and undergo training.

Perhaps the best example of this reluctance in the face of great promise is offered by Christopher Reeve, the actor who has been a crusader for medical research in the years after an equestrian accident left him paralyzed to such an extent that he was unable even to breathe on his own. Last year, Reeve received a great deal of media attention as a result of improvements in his condition. Since his injury, he has regained the ability to move his right wrist, the fingers of his left hand, and his feet. He can also feel a pinprick on most parts of his body.

Reeve has given a lot of credit to his activity-based rehabilitation, which includes electrical-stimulation exercise sessions, with electrodes placed on the surface of the skin rather than being implanted. He uses daily electrical stimulation to build mass in his arms, quadriceps, hamstrings, and other muscles. Part of his regimen is riding a stationary bicycle, which uses electrical stimulation to activate his leg muscles in the proper sequence to push the pedals.

But despite his support for electrical stimulation as part of the exercise process, Reeve has never strongly advocated FES as a long-term solution to paralysis. He has been much more active in supporting more glamorous approaches to neurological disorders, including stem-cell therapies and spinal cord regeneration research.

"There's been a trend to fund research on a cure and basic science relating to spinal cord injury at the expense of care research," says the physiatrist Kirshblum. "This is a problem for our specialty and the disabled community. Spokespeople for the spinal cord injury community haven't done enough to promote FES. Those fighting for a cure have been more vocal."

Many neural engineering researchers complain that the high-profile Christopher Reeve Paralysis Foundation in Springfield, N.J., which funds research related to spinal cord injury, has given short shrift to the development of FES systems that could restore at least some function to many people with paralysis sooner. For example, neural prosthesis research received less than 7 percent of the $1.8 million of grant awards in the foundation's most recent cycle. And visitors to the Christopher and Dana Reeve Paralysis Resource Center Web site (http://www.paralysis.org) find little FES information.

Susan Howley, director of research for the Christopher Reeve Paralysis Foundation, acknowledged research toward a cure for paralysis has been a paramount goal of the organization. "Spinal cord regeneration has been the Holy Grail," she says. But, she adds, the foundation now places more emphasis on rehabilitation technologies, including neural prostheses. "We now know that rehabilitation does more than preserve muscle and bone," she says. "It may play a role in teaching the spinal cord after an injury. And every future spinal cord injury therapy will involve rehabilitation in some way."

Howley says she had not seen a large number of funding requests from neural prosthesis researchers, but would be open to consid-

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ering them, especially those for devices addressing so-called concomitant functions, like bowel function and sexual function.

Last year, Reeve himself became something of an implant convert when he acquired a phrenic nerve stimulation system, which controls his diaphragm and dramatically reduces his dependence on a mechanical ventilator. Working through a laparascope, surgeons placed electrodes in Reeve's diaphragm muscles. The electrodes are attached through wires under the skin to a small external battery pack, which electrically stimulates the muscle and the phrenic nerves, causing the diaphragm to contract and air to enter the lungs.

The system was developed at Case Western Reserve University, Cleveland, Ohio, and is now marketed by Synapse Biomedical Ltd. of Oberlin, Ohio. Reeve's decision to go ahead with the implantation not only provided a good measure of public exposure for neural engineering, it also raised the hope that other neural engineering projects would attract more interest from Reeve's foundation.

HUNTER PECKHAM, director of the Cleveland Functional Electrical Stimulation Center, which developed French's standing prosthesis, laments the "defeatist" attitude he and his colleagues often confront when describing the new system to patients—the result, in part, of an ingrained abhorrence of implanted devices. But resistance and mistrust of medical devices is nothing new, according to Alfred Mann, the founder of several implantable device firms.

Some physicians fear their patients will be used as guinea pigs to test DANGEROUS DEVICES

The hurdles FES faces may be a little different, though. It is particularly telling to contrast FES's image with that of pacemakers and defibrillators. Implanted cardiac devices are a $5 billion business and are broadly accepted. IEEE Fellow Charles Robinson, a professor of biomedical engineering at Louisiana Tech University, in Ruston, suggests that the difference lies in the fact that cardiac devices are viewed as saving lives, while FES is thought just to improve the quality of life, even though the principal outcome of cardiac stimulators is a quality-of-life improvement.

Engineers who developed the first generation of cochlear implants are familiar with the phenomenon. When the first commercially available systems reached the market in the past decade, vendors faced an onslaught of opposition from a most unlikely source: the deaf community itself. Many deaf activists complained that restoring hearing to deaf people would rob them of their identity and threaten to shake the cultural bonds formed by the medium of choice in the community, sign languages. Today, though, after the implants have provided some degree of hearing to over 70 000 people around the world, resistance from within the deaf community has withered.

Ingrained aversion to implants, however, may be overcome by making them less of a burden to use and implant. A good example is the Bion injectable microstimulator, marketed by Advanced Bionics Inc. [see illustration, "Injectable Implant"]. Implants for moving paralyzed limbs usually require threading leads between the nerves and muscles to be stimulated and an implanted pacemaker-like control device, which provides the electrical impulses to trigger muscle contractions. Bion does away with the leads and the implanted controller. Originally developed by collaborating researchers at the Alfred Mann Foundation, Queens University, in Canada, and Illinois Institute of Technology, the device measures just 16 millimeters long by 2.4 mm in diameter and is powered and controlled by radio-frequency signals from a coil embedded in an article of clothing. It operates using less than 500 milliwatts of power.

Because the Bion is so small and has no leads, it can be injected into nearly any part of the body through a standard 12-gauge needle and a catheter during an office visit. The developers believe it will go a long way toward countering objections that clinicians and patients might have to more cumbersome stimulation systems. Indeed, Mann is planning to launch a new device firm that uses Bion technology to treat paralysis caused by spinal cord injury and stroke.

Joe Schulman, president of the Alfred Mann Foundation, Valencia, Calif., and one of the developers of the Bion, envisions a neural prosthesis constructed using multiple Bions injected into key muscle groups, communicating with one another and with controlling electronics via an RF transceiver in each device.

Another bright spot in the FES scene is the growing number of research groups and companies developing neural devices to restore sight in the blind. Mann also founded a neural prosthesis firm in 1998 called Second Sight, in Sylmar, Calif., which is developing a retinal implant to treat blindness caused by retinitis pigmentosa or macular degeneration. The device receives visual signals from an external camera worn on the head. The signals are sent wirelessly to an implanted receiver, which activates electrodes on the surface of the retina, at the back of the eyeball. Last year, researchers at the University of Southern California, in Los Angeles, implanted a 16-electrode array made by Second Sight in a blind volunteer. Although the resolution was crude, the volunteer could tell light from dark and identify basic shapes.

The Second Sight approach is not the only effort to develop a visual prosthesis. IIP-Technologies in Bonn, Germany, for example, is developing a retinal implant with a wireless link to an external imaging system. There are also several research teams working on a visual prosthesis that bypasses the eye altogether. It feeds signals from an external camera directly to the neurons in the back of the brain that would ordinarily get signals from the retina.

The use of technologies similar to FES to treat common neurological problems, such as stroke, chronic pain, and Parkinson's disease may also raise the profile and acceptability of FES. Market leader Medtronic Inc., Minneapolis, Minn., has done a brisk business with its Activa deep-brain-stimulation system for treating Parkinson's and other tremors since the device was approved by the U.S. Food and Drug Administration last year. The treatment quickly gained support from government and private medical insurers.

Optimistic financial outlook aside, many neural engineers would be happier if their technology could be put to use first in the seriously disabled communities that need them the most, regardless of their market size. And if Jennifer French fulfills her new mission, that might just happen. ■

TO PROBE FURTHER

IEEE Transactions on Neural Systems and Rehabilitation Engineering is the leading publication for technical material about functional electrical stimulation.

Jennifer French's Web site is at http://www.theSTIM.org.

The author's publication, *Neurotech Business Reports*, can be found at http://www.neurotechreports.com/.

Go to Spectrum Online for more on neurotechnology.