NEWS

Can Sensors Make a Home in the Body?

Researchers dream of implanting sensors and other devices that interface with the body's biochemistry to treat diseases such as diabetes and even predict coming ailments. The immune system, however, is not so keen

In early May, Jeff and Leslie Jacobs and their 14-year-old son Derek took a small step toward humanity's cyborg future. The Jacobses became the first people to receive tiny computer chip implants that store medical data, similar to the chips implanted in pets to identify them if they are lost. Jeff Jacobs, a 48-year-old dentist, has fought off numerous illnesses including cancer and a degenerative spinal condition, and he currently takes 10 different medications. He hopes that the chip under the skin of his upper arm could provide doctors with a detailed medical history in an emergency.

Implanting things in the body is nothing new, of course. Artificial hips and pacemakers have been around for decades, and researchers have long dreamed of making everything from bionic arms, ears, and eyes to long-surviving artificial hearts. Most of those dreams of integrating the artificial with the biological still remain more fiction than science. But some might be on the verge of becoming real.

By fits and starts, researchers and companies are beginning to devise "smart" implantable sensors that develop biochemical interfaces and in some cases respond to changes in the body. If successful, the novel implants could track early signs of diseases such as cancer, vastly improve the ability of people with diabetes to monitor and control their blood glucose levels, and even monitor internal healing following surgery. Implanted sensors, says Mauro Ferrari, a biomedical engineer at Ohio State University, Columbus, will enable doctors to continuously scan our bodies for signs of disease and begin treatment even before symptoms appear. "They will dissolve the barriers we have between diagnostics and therapeutics," he says.

But Ferrari and virtually all others who are working to develop implantable biosensors agree that success isn't coming quickly or easily. The key challenge is that virtually every implanted material triggers the body's defenses to wall off and isolate nonnatural materials, making a sensor essentially blind to the biochemistry outside those walls. And even if researchers overcome that hurdle, financial and ethical obstacles are lying in wait. Even so, many researchers are optimistic. The time when we all have some artificial device implanted in our bodies might be slow in getting here, says Jeffrey Borenstein, a biosensors expert at the Massachusetts Institute of Technology. However, he says, "I think the day is coming."

Taken to extremes. *Star Trek*'s half-machine, half-human Borg featured biosensors run riot.

Sweet sensation

The dream of reaching this day goes back centuries. Ever since Mary Shelley unleashed *Frankenstein* on the literary world in 1818—at the height of the Industrial Revolution—fiction writers have imagined constructing humans using the technology of their day. Recent fictional mergers of implants with biology range from the *Six Million Dollar Man* to the villainous Borg characters of *Star Trek: The Next Generation*.

For today's real-world sensor developers, the big carrot is finding a way to let people with diabetes measure their glucose level without having to prick their finger to get a drop of blood. Diabetes now afflicts some 16 million Americans, and the test strips for analyzing those drops of blood are a $2-billion-a-year business.

Biosensing companies have long hoped to tap into that market. In the mid-1990s, two companies—Futrex Medical Instrumentation and Biocontrol Technology—made a high-profile push to produce the first noninvasive glucose sensors, using techniques such as shining infrared beams through the skin. But their products proved too unreliable for the U.S. Food and Drug Administration and wound up costing investors hundreds of millions of dollars. "This field has a checkered history," which poisoned the water for many sensor developers, says Russell Potts, who heads research at Cygnus, a California company developing a new glucose-monitoring system.

Sensor designers realized that it was going to be necessary either to extract some bodily fluid or to go in and make the measurement in situ. But then they ran up against the problem that bedevils everyone who tries to make implanted biosensors: the immune response. Once any artificial material enters the body, a natural inflammatory response immediately kicks in, coating the intruder's surface with thousands of proteins and marshaling immune sentries called neutrophils and macrophages to remove it.

When that can't be done, as in the case of a medical implant, the cells in this first wave typically merge and release a cascade of signaling proteins called chemokines and cytokines, which summon fibroblasts and other cells into the area. Within days, the newcomers form a tight-knit capsule around the implant, sealing it off from the rest of the body and making it virtually impossible for the sensor to track the surrounding biochemistry. Outwitting this natural immune response "is the most formidable challenge in this area," says David Grainger, a chemist at Colorado State University, Fort Collins.

One solution is to pull out the sensor before the fibrous capsule forms around it. In 1999, for example, Northridge, California–based Medtronic MiniMed began selling a tiny enzyme-based sensor that is implanted for up to 3 days at a time under the skin, where it measures glucose in the fluid that surrounds cells in skin tissue. The sensor is wired to a readout device outside the body

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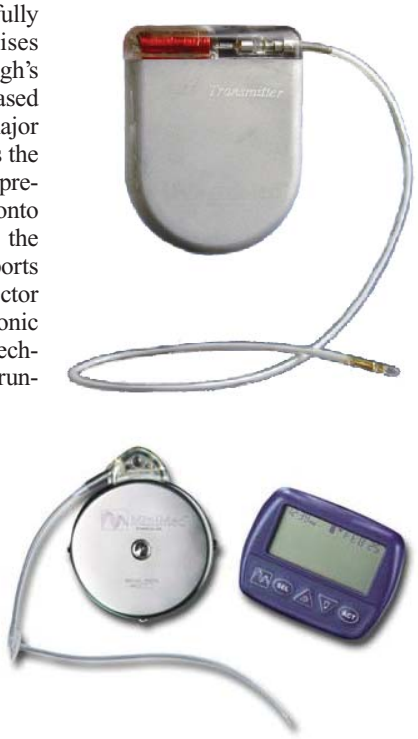
and performs steadily until the body seals it off. Still, from a user's point of view, the Medtronic sensor is less than ideal. Users must have new sensors inserted every few days, making them impractical as permanent glucose monitors. And because only part of the sensor is implanted, there is always a risk of infection.

Going inside

At the University of California, San Diego, David Gough and colleagues have pioneered an alternative that is fully implantable and promises longer term results. Gough's team implants enzyme-based glucose sensors in a major vein of the heart and uses the steady flow of blood to prevent cells from grabbing onto the sensor and forming the capsule. A radio link reports glucose levels to a detector outside the body. Medtronic has licensed Gough's technology and is currently running clinical trials on an artificial pancreas that combines the venous sensor with an implanted pump that automatically delivers insulin based on the sensor's readings. Still, others remain cautious about the technology, fearing that if a clot should form around the sensor and become dislodged, it could make its way to the lungs and create a life-threatening embolism. Gough acknowledges the concern but says he believes that for some patients the benefit will be worth the small risk.



Diabetes made easy. An implantable blood-glucose sensor (*top*) and insulin pump (*bottom*).

For many researchers, the real hope for implanted biosensors lies not in evading the body's immune response but in trying to shape and control it so that artificial materials can be integrated into the body more naturally. "The Holy Grail of this business is the tissue-implanted probe, where the interface between the artificial and biological material resembles the biological tissue," says William Reichert, a biomedical engineer at Duke University in Durham, North Carolina.

That's the grail Kenneth Ward and his colleagues at Legacy Health System in Portland, Oregon, are seeking with their glucose sensor that can be implanted under the skin for long periods. To get around the encapsulation issue, Ward's team adds a protein called vascular endothelial growth factor (VEGF) to the wound site when the sensor is implanted. VEGF is a signaling molecule that triggers the production of blood vessels. In work with rats, Ward's team has found that adding VEGF to the site near a biosensor significantly increases the number and density of blood vessels in the surrounding tissue. "We're hoping that will allow glucose and oxygen from the blood to reach the sensor and improve the sensor lifetime," Ward says. The company is still carrying out studies to confirm the effect, he adds.

Francis Moussy of the University of South Florida, Tampa, agrees that adding VEGF is a good way to go. But he is concerned that a one-time infusion of the protein will not produce a lasting effect. "As soon as you stop the delivery of VEGF, the blood vessels will disappear," Moussy says. So his group is developing a way to add a VEGF-producing gene to cells in the wound site to coax them into pumping out VEGF for months at a time. Moussy's team is also experimenting with coating the outside of its biosensor with a steroid called dexamethazone, which dampens the natural inflammatory response. Early-stage trials with animal models show that both the gene therapy and steroid seem to work separately, and now Moussy's team is working to put the two together.

Others, however, are concerned about the use of VEGF. "It's dangerous," says Buddy Ratner of the University of Washington, Seattle. Although VEGF is a natural part of wound healing, overproduction of the protein has been implicated in everything from cancer to diabetic retinopathy, a condition in which blood vessels overgrow the retina and disrupt vision, Ratner says. Ward responds that if care is taken to ensure that VEGF remains in its local environment, rather than entering the wider blood circulation, then it's doubtful that problems will arise. But Reichert adds that VEGF isn't the only protein worth trying. Dozens of cell-signaling molecules are part of the natural response to injury, including growth factors called interleukins, Reichert says. He suspects that in time researchers will use a cocktail of these molecules to help integrate biosensors into the body.

Taking the strain

Although glucose monitoring might promise the biggest payoff, other applications of in situ sensing are starting to gain attention as well. Micromechanics expert Shuvo Roy of the Cleveland Clinic Hospital in Ohio, for example, recently launched a project to create tiny pressure sensors that can be implanted during spinal surgery when neighboring vertebrae are fused together. Doctors fuse vertebrae for patients who have problems with the spongy discs that separate the bones in the spine. They then carry out ultrasound tests to ensure that the vertebrae fused properly. But in about 15% of cases, those readings are incorrect and often lead to another surgery.

In hope of eliminating the unneeded follow-up surgeries, Roy's team is crafting a microelectromechanical sensor to monitor the load being carried by the bones in the spine. The sensor contains a microscale rod that a surgeon connects to two vertebrae before grafting bone into the same region. As that bone fuses with the neighboring vertebrae, it takes over the load-bearing duties of the rod in the strain gauge, which transmits the changes in pressure to a radio receiver outside. So far Roy's team is still testing the system on goats. However, he says, "our preliminary assessment is it's not going to be a problem. We have not seen a toxic reaction in the site." And because the sensor does not read biochemical signals, it shouldn't matter if immune cells wall it off from the body. Ultimately, Roy hopes to shrink the sensors to less than a cubic millimeter so that they can be implanted with a syringe.

For any of these devices to make a difference in people's lives, it will take more than just technical success, says Amy Pope-Harman, a lung transplantation expert at Ohio State University Medical Center in Columbus. Pope-Harman says she watches effective medical technology stumble all the time because it either doesn't mesh well with the way doctors practice medicine or because insurers won't cover the costs. Implantable biosensors will likely face both problems, Pope-Harman says. Will doctors have to be available 24 hours a day to respond to warnings from biosensors in their patients? And what if patients keep biosensor results secret from their doctor? Such real-world questions are only now beginning to emerge as the technology starts to show real promise.

"We're a long way from *Fantastic Voyage* or the totally invaded body," Pope-Harman says. But perhaps we're not so far from the first brief excursions.

–ROBERT F. SERVICE

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