Surgeons have implanted a new prosthesis in four patients to correct disabling dizziness.

CONQUERING VERTIGO

The device may someday restore balance to hundreds of thousands more

By James Phillips

One day in 2009 Robert Milner (not his real name), a lawyer and avid outdoorsman, was driving on a highway through the mountains of Washington State when he sensed he was tumbling sideways. Had his car flipped, propelled perhaps by an unseen T-bone collision? Milner slammed on the brakes. The car stopped—but not upside down. It sat fully upright in the middle of the highway. There Milner stayed, stuck in his mental tailspin, until the highway patrol arrived.

Such attacks of vertigo, the sense that you are moving when you are not, were not foreign to Milner. He had been having them every few days. One time he collapsed onto the courthouse steps in his suit, the world spinning as he lay on his side, nauseated and unable to move, until somebody called 9-1-1 and paramedics helped him into an ambulance.

For three years Milner's life had been literally turned upside down by a disorder affecting a small set of structures in the inner ear known as the vestibular labyrinth. This system of organs, which is next to the one that allows us to hear but separate from it, underlies our sense of how our head is oriented and moving. Although few people give it much thought, it is essential to normal function. Knowing which way is up is critical for balance, posture and locomotion. Sensing how your head is turning stabilizes your vision: when your head rotates one way, your vestibular system moves your eyes in the opposite direction so that what you are looking at remains stable. This action is called the vestibulo-ocular reflex.

When something goes awry with these inner ear organs, the world may spin or flip, vision may blur, and you may wobble or even fall. Because of the connections between the vestibular system and other brain regions, you also often vomit and get confused. Inner ear troubles may stem from ear infections, autoimmune disorders, head trauma, or treatment with certain antibiotics or cancer drugs. In Milner's case, for unknown reasons, pressure periodically built up inside one inner ear, rupturing the membranes of its component structures and shutting down their function.

Although Milner's disorder, known as Ménière's disease, is rare, affecting just 12 out of every 1,000 people, inner ear difficulties are quite common. About one in three people experiences disturbing dizziness at some point in their life because of illness, injury or drug treatment. For most of us, these symptoms, while dramatic, will be short-lived. Either the inner ear recovers, or it retains sufficient function for the brain to adapt.

Yet for perhaps one eighth of those with severe inner ear injury, the changes are too great for the brain to fully compensate for the loss of function. These individuals experience chronic unsteadiness for the rest of their life. In addition, insults to the inner ear can add up over the years, leading to balance problems in 70 to 80 percent of the elderly, in whom falls are also the chief cause of fatal injuries. For the vast majority of individuals with chronic vestibular loss, there is no effective way to restore their lost function.

In fact, for many cases of vertigo the main treatments involve the exact opposite: shutting the system down. So about eight years ago my colleagues and I at the University of Washington set out to develop an inner ear prosthesis that might restore balance and a sense of orientation to patients such as Milner and others who have sustained damage to the vestibular system.

Inertial Guidance

The brain's vestibular network serves as the body's inertial guidance system. It takes information from several sensory modalities, including vision, touch and muscle sense (kinesthesia), and uses it to help the mind compute the body's physical place in the world. Its primary sensory structure is the vestibular labyrinth, which contains five organs that relay information about head motion to the brain. Three semicircular canals, which look like tiny Hula Hoops oriented at right angles to one another, reveal the rotation of our head in three dimensions; two saclike otolith organs tell us how the head is oriented with respect to gravity and if it is moving linearly up, down or sideways.

If you turn in any direction, you will activate some combination of semicircular canals; if you lean to one side or move in a straight line, the otolith organs will spring to life. These organs are filled with fluid and contain receptor cells whose fine hairs project into a gelatinous tongue or layer (depending on the organ) within that fluid. When the head moves relative to the fluid or gel, the hairs bend, activating the receptor cells to which they are attached and sending signals to the brain.

All the hair cells in a given semicircular canal have the same orientation within the gelatinous tongue and so send identical directional information to the brain: they signal rotation in the plane of that canal [*see illustration on page 00*]. Any time you rotate your head, you trigger some combination of activation in the three canals on each side of the head, with the direction of motion coded in

Fast Facts

LOSING YOUR BEARINGS

1. One in three people experiences disturbing dizziness at some point in their lives resulting from illness, injury or drug treatment.
2. Insults to the inner ear can add up over the years, leading to balance problems in up to 80 percent of the elderly, in whom falls are also the chief cause of fatal injuries.
3. An experimental inner ear prosthesis can restore balance and a sense of direction to patients who have sustained serious damage to the vestibular system.

When something goes wrong with the organs of your inner ear, the world may spin or flip, vision may blur, and you may wobble or even fall. You also often vomit and become confused.

their relative signaling rates. So if you move your head up and then to the left to observe a passing butterfly, both your posterior canals will respond vigorously to the upward motion. At the same time, cells in both anterior canals will quiet down. Turning to the left will spur strong signals from your left horizontal canal and blunt the response from the right one.

The canals are oriented in complementary pairs in either ear, with any motion increasing the signaling rates from some canals and decreasing the signaling rates from the complementary canals in the opposite ear. The brain deduces the speed of the motion from the frequency of the signals from each canal. If you whip your head to the right, for example, the hairs in the canals in your right ear will bend dramatically, producing more frequent nerve signals from those canals and less frequent nerve signals from the canals in your left ear. These signals are sent to the brain, which has the job of making sense of them.

In the otolith organs, hairs from the receptor cells project up into a gelatinous matrix. At the top of the matrix are calcium carbonate crystals called otoliths. A tilt of the head causes the otoliths to fall to one side, as if they were fruit atop a pan of gelatin. The movement bends the gelatin and the hairs of the embedded hair cells. Moving the head vertically or horizontally moves the hair cells up and down or sideways under the crystals, which lag behind, again bending the gel and the hair cells. In this way, these organs detect linear motion and tilt.

In people who have no vestibular information, a condition typically caused by a drug that is toxic to hair cells, objects seem to move whenever the head moves, as if the person were looking at the world through a shaking video camera. Balance is severely compromised, causing these individuals to stumble as if they were drunk or to take short shuffling steps. In these cases, a simple task such as going to the mailbox becomes an almost insurmountable challenge. Because the vestibular system connects to parts of the brain that govern working memory and concentration, patients also may have trouble thinking clearly, focusing or remembering events and locations. Each day is like floating in the ocean, with both thoughts and physical sensations similarly unanchored.

For these individuals, canes and walkers act like hearing aids, providing additional sensory input from touching the ground. The devices do not speed up or normalize their users' gaits, however; nor do they allay the sense of disorientation and physical detachment that often accompany the condition.

Lopsided damage to the vestibular system, which is the more typical consequence of disease or trauma, can be even worse, producing nausea and dramatic illusions of being in motion. Damage to just one ear also produces the extreme vertigo that people with Ménière's disease experience.

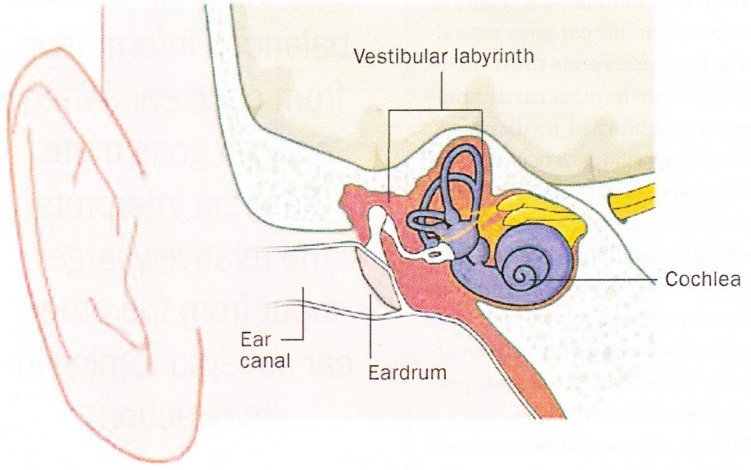
When we are motionless, the brain expects balanced vestibular information

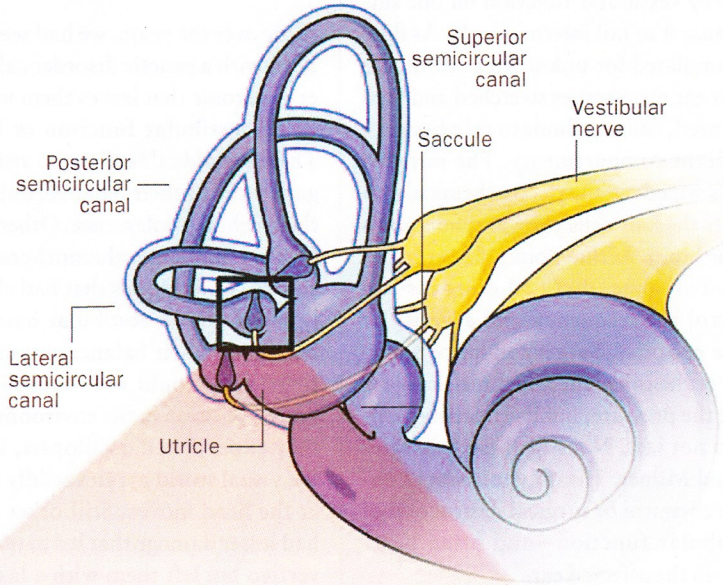
Knowing Which Way Is Up

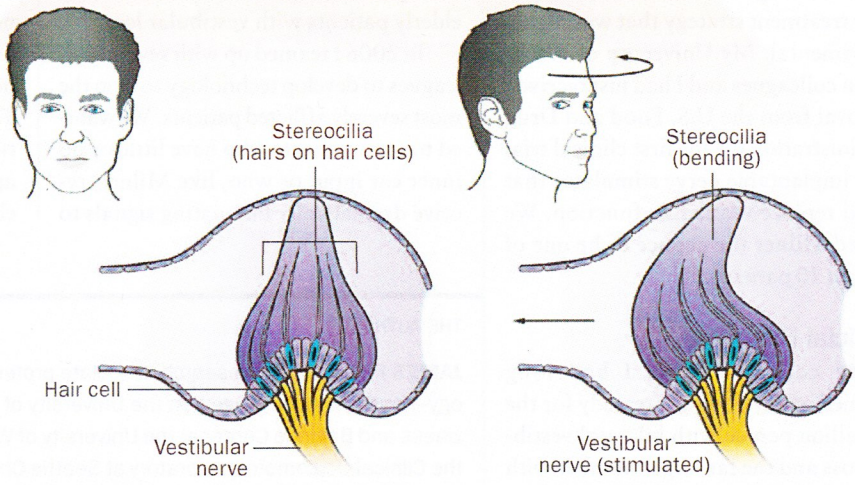
Many people think the ears are only for hearing. But our ears contain organs that are critical to our ability to sense how we are oriented in the world, to see clearly, and to balance. These structures make up the vestibular labyrinth. They are located near the cochlea, the hearing portion of the inner ear, but serve distinct functions.

Among these vestibular organs are three semicircular canals (superior, posterior and lateral), which sit at right angles to each other. Their job is to sense head rotatation in three dimensions. When the head turns, fluid inside the canals moves and jostles a gelatinous substance into which the hairs (called stereocilia) from sensory cells project. The bending of the hairs then causes the hair cells to send signals through the vestibular nerve to the brain. Sensing head rotation is critical for vision: the eyes must compensate for such motion or our surroundings will appear to shake with every turn of the head.

The two other vestibular organs are the utricle and the saccule. These sac-like structures tell us how we are oriented relative to the pull of gravity; they thus allow us to detect head tilt and linear motion. In these organs, the hairs of the receptor cells are embedded in a gelatinous layer topped by calcium carbonate crystals. Tilting the head makes the crystals fall to one side, causing both the gelatin and the stereocilia to bend. Lateral movement shifts the crystals horizontally or up and down, again distorting the stereocilia and eliciting a response from the sensory cells.







from each ear. Motion toward one ear creates an imbalance, with more input coming from that ear and less from the other one. So when one ear goes virtually mute, the brain interprets the relatively larger input from the other ear as a rapid turning or tumbling in its direction. The illusion is impervious to reason. Even if you know you cannot possibly be moving, you still feel as if you are spinning or somersaulting through space. Meanwhile the brain activates reflexes that violently empty the stomach, in case you were poisoned, and hurls the body toward the affected ear to "save" you from your presumed fall in the other direction.

For Milner, disease did not so much destroy vestibular function on one side as cause it to fail intermittently. As fluid accumulated for unknown reasons, his inner ear membranes stretched and then ruptured, causing fluids to mix between different compartments. The mingled fluids wiped out the electrochemical gradients the hair cells need to send signals to the brain. At that point, the ear fell silent. For some, diet and diuretics can control the frequency and severity of these episodes. Surgery to lance a portion of the inner ear membrane may relieve the pressure, but its effects typically do not last. None of these strategies helped Milner. His only remaining option: chemical or surgical destruction of vestibular function—and often hearing—in the affected ear.

As the lawyer prepared for surgery in 2010, his surgeon told him about one other treatment strategy that was highly experimental. My University of Washington colleagues and I had just received approval from the U.S. Food and Drug Administration for the first clinical trial of an implantable nerve stimulator that would replace vestibular function. We offered Milner the chance to be one of our first 10 patients.

Artificial Dizziness

My colleagues and I had long dreamed of developing a remedy for the six million people with bilateral vestibular loss and the far larger number with uncompensated single-sided loss. In our clinic over the years, we had seen people born with a genetic disorder called Usher syndrome that leaves them with little or no vestibular function or hearing. These individuals at first use vision to regain some of their balance, only to lose their sight in adolescence. Other patients of ours had had chemotherapy or a course of antibiotics that had chemically killed all the vestibular hair cells in both ears. Their balance was extremely poor; they could not determine their body's position in the environment, and they experienced oscillopsia, in which the visual world gyrates wildly whenever the head moves. Still other patients had lesser damage that led to temporary vertigo but left them with a lasting unsteadiness and disorientation. Such amorphous symptoms also afflict many elderly patients with vestibular loss.

> When we are motionless, the brain expects balanced information from each ear. When one ear goes mute, the brain interprets the relatively larger input from the other ear as rapid turning in its direction.

In 2006 I teamed up with several colleagues to develop technology to help the most severely afflicted patients. We wanted to treat patients who have little or no inner ear input or who, like Milner, receive dramatically fluctuating signals to which the brain cannot adapt. Our group, which included neuroscientists, biomedical engineers and an inner ear surgeon, applied to the U.S. National Institute on Deafness and Other Communication Disorders to build and test a device.

We were far from the first to float this idea. In fact, back in the 1960s neuroscientists Bernard Cohen and Jun-Ichi Suzuki, both then at Mount Sinai Hospital in New York City, had implanted wires in the inner ears of cats and monkeys and showed that by sending current through the wires, they could produce naturally appearing eye movements in different directions, similar to those seen during head movements. More recently, research teams at Harvard University and Johns Hopkins University had been working on small, fully implantable stimulators attached to motion sensors that stimulate the inner ear during head movement, but their devices were not yet ready to be implanted in people.

Like these other experimental prosthetics, ours would stimulate the semicircular canals only. The hair cells in the otolith organs are positioned in a variety of orientations, leading to an array of signals encoding direction of motion that would be more complex to recapitulate. Our approach was different from the others in one important respect, however. Instead of building a device from scratch, we planned to adapt the robust and proved technology used in cochlear implants. Cochlear implants generate electrical pulses that activate the auditory nerve to restore hearing. Similarly, our device would stimulate the vestibular nerves to restore orientation and balance. The implanted stimulator would be identical to one that was already tested and approved in humans; we would simply change the electrodes and programming

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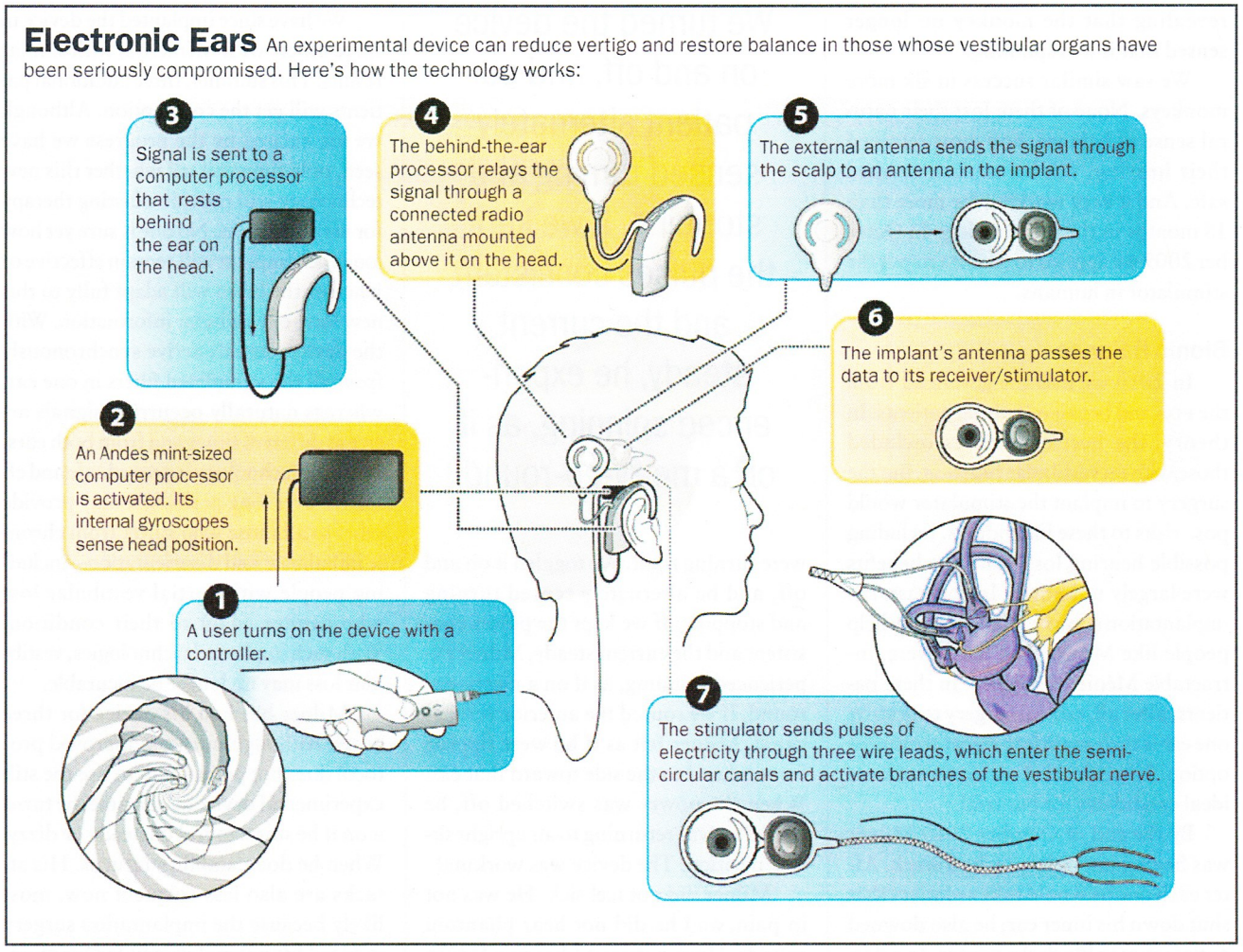

of the device to suit its new application.

On August 1, with funding secured, we began working in earnest on the various parts of the device. A system of three tiny gyroscopes would align with the semicircular canals to sense head motion. These gyroscopes would sit outside the head, encased along with a computer processor in a box the size of an Andes thin mint. The processor's job would be to translate the information from the gyroscopes into radio waves, which it would transmit to the stimulator implanted behind the ear in the temporal bone of the skull. The stimulator would then send its signals through three leads, each of which would tunnel into a separate semicircular canal [*see illustration above*].

Our electrode leads had to be far tinier than those in the cochlear implant—narrower than one fifth of a millimeter and less than 2.5 millimeters long—to fit in the bore of each semicircular canal. We programmed our coin-sized stimulator to deliver pulses of electricity that would become more frequent as the head moved faster toward the implanted ear and slower as the head turned more rapidly away from that ear. Our program also varied the stimulation of the nerves from each semicircular canal by the plane of the rotation—its horizontal, or yaw (turning left to right), vertical, or pitch (nodding up and down), and lateral, or roll (tilting from shoulder to shoulder), components.

By the end of 2006 we had a prototype. We tested its fit and durability by implanting it in skulls from animal and human cadavers. In October 2007 we put it in a living monkey. We turned it on and watched the monkey's eyes. If the device worked, the eyes would move in the opposite direction of the movement encoded by the stimulation, triggered by the vestibulo-ocular reflex. To our disappointment, however, the monkey's eyes stayed put.

Then, in spring 2008, our surgeon, Jay Rubinstein, decided to subtly reposition the electrodes, shifting them just a few millimeters within the inner ear. When the switch was flipped, the monkey's eyes moved! We turned off the juice; the eyes stopped. We ramped it up, and the eyes moved faster. We changed which nerve received stimulation, and the eyes changed direction. In short, we successfully created all manner of artificial dizziness in this animal. We also did the opposite and made the monkey immune to vertigo. As the monkey spun around in a movable chair, as if in an amusement park ride, we turned on the prosthesis—and its eyes stopped moving,

revealing that the monkey no longer sensed that it was spinning.

We saw similar success in six more monkeys. None of them lost their natural sense of balance, and most retained their hearing, so the implant seemed safe. And it kept working for more than 18 months in the first monkey. In October 2009 we applied to the FDA to put the stimulator in humans.

Bionic Balance

In 2010 we had the go-ahead from the FDA and began recruiting patients. In theory, the best candidates included those with no vestibular function. But the surgery to implant the stimulator would pose risks to these individuals, including possible hearing loss—and the benefits were largely unknown. In contrast, the implantation surgery might actually help people like Milner who had severe, intractable Ménière's disease. In these patients, after all, radical surgery to destroy one ear is their main last-resort treatment option. So we decided such patients were ideal candidates for our trial.

By the end of October 2010 Milner was having multiple attacks a week. After each one he would take sedatives that shut down his inner ear; he also downed antiemetics to block the nausea. In a day, he would recover, as would his inner ear membranes—only to rupture again within a couple of days. Milner just wanted it to stop, as his life shut down every time his ear did. He volunteered to be our first patient. He hoped not only to get relief from his condition but also to help others who suffered as he did.

After six hours in the operating room, the surgeon stitched up Milner's ear. Milner recovered rapidly and went home the next day. A week later he returned to our laboratory for testing. We fastened a headband containing the external processor and strapped him to a clinic bench with a seatbelt. We worried he would become nauseated or disoriented, hear loud sounds or feel facial pain. Then we turned on the stimulator for the first time.

We stimulated the horizontal canal on the right side—and Milner's eyes moved left. In the dark, he felt as if he were turning right. We toggled it on and off, and he alternately sensed turning and stopping. If we kept the pulses consistent and the current steady, Milner experienced spinning, as if on a merry-go-round. If we roused the anterior vertical canal, Milner felt as if he were tipping forward and to the side toward that ear. When the power was switched off, he sensed he was returning to an upright sitting position. The device was working!

We turned the device on and off, and our patient alternately sensed turning and stopping. If we kept the pulses consistent and the current steady, he experienced spinning, as if on a merry-go-round.

Milner did not feel sick. He was not in pain, and he did not hear phantom sounds. He experienced hearing loss in the implanted ear, but this outcome was the same as the alternative surgery would have produced. On other visits, we have asked Milner to walk, turn his head and balance on a wobbly platform. With the help of the device, his balance improves, and he is steadier as he moves.

We have since implanted the device in three others with Ménière's, with similar results. This summer, three additional patients will get the contraption. Although we are excited by the progress we have seen, only time will tell whether this new technology will provide a lasting therapy for vestibular loss. No one is sure yet how long each implant will remain effective or whether the brain will adapt fully to this new form of vestibular information. With the device, signals arrive synchronously from all the stimulated fibers in one ear, whereas naturally occurring signals arrive at different times and from both ears. But if the technology is proved safe and effective over long periods, it may provide relief to all those who suffer from chronic imbalance and disorientation—including people with partial vestibular loss who cannot adapt to their condition. With such implanted technologies, vestibular loss may no longer be incurable.

Milner has had his device for three years. Although our FDA-approved protocol does not permit him to use the still experimental device all the time, he turns it on if he starts to feel unsteady or dizzy. When he does, stability returns. His attacks are also less frequent now, most likely because the implantation surgery reduced his natural vestibular function. For both reasons, his life is vastly richer and easier than it was before he received his prosthesis. Earlier this year he sent us a digital photograph from a recent ski trip. He stood at the top of a run at his favorite ski resort. A sign in the picture noted the name of the trail: "Vertigo." M

FURTHER READING

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- **Regaining Balance with Bionic Ears.** Charles C. Della Santina; *Scientific American,* April 2010.