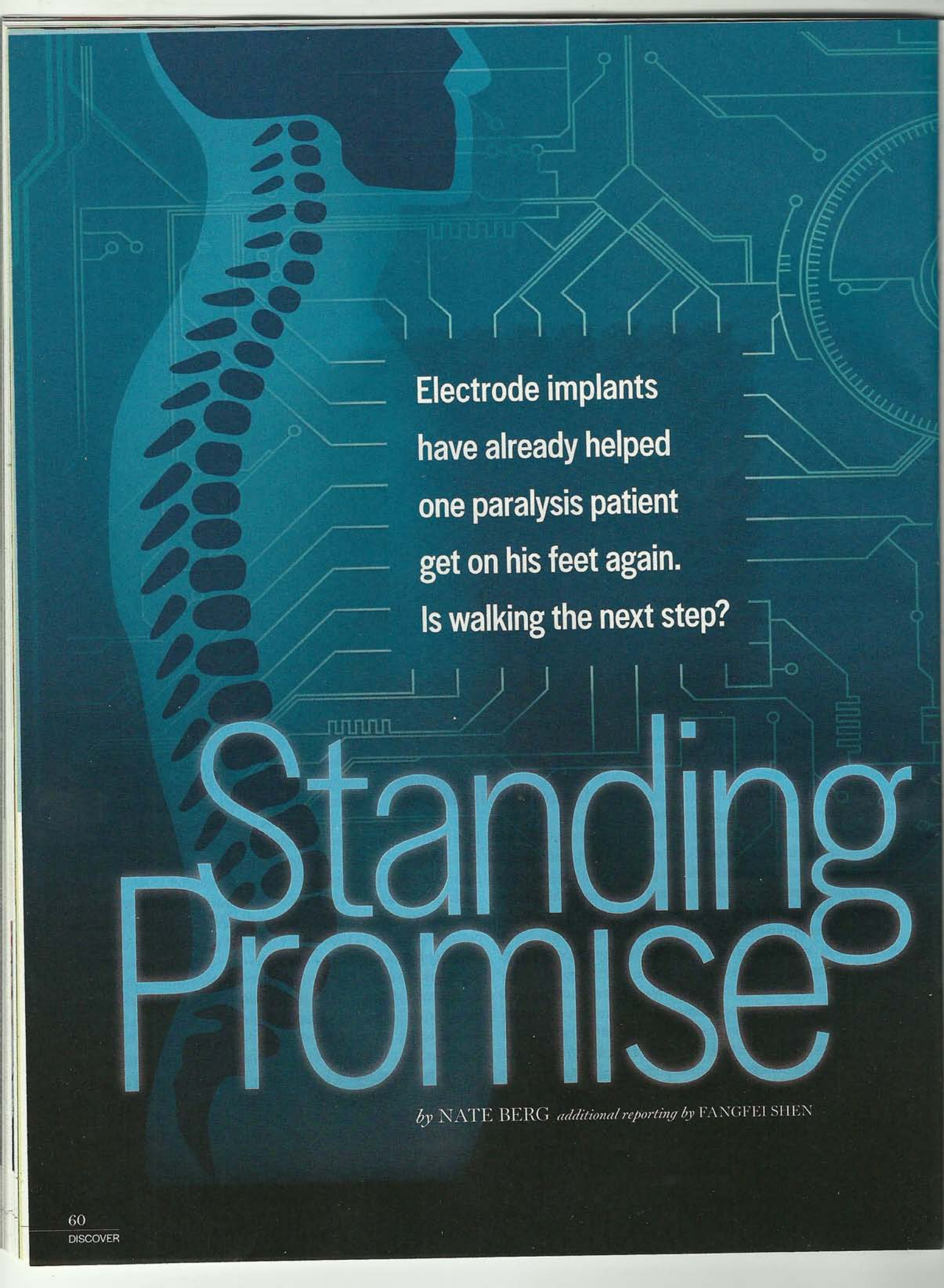


Electrode implants have already helped one paralysis patient get on his feet again. Is walking the next step?

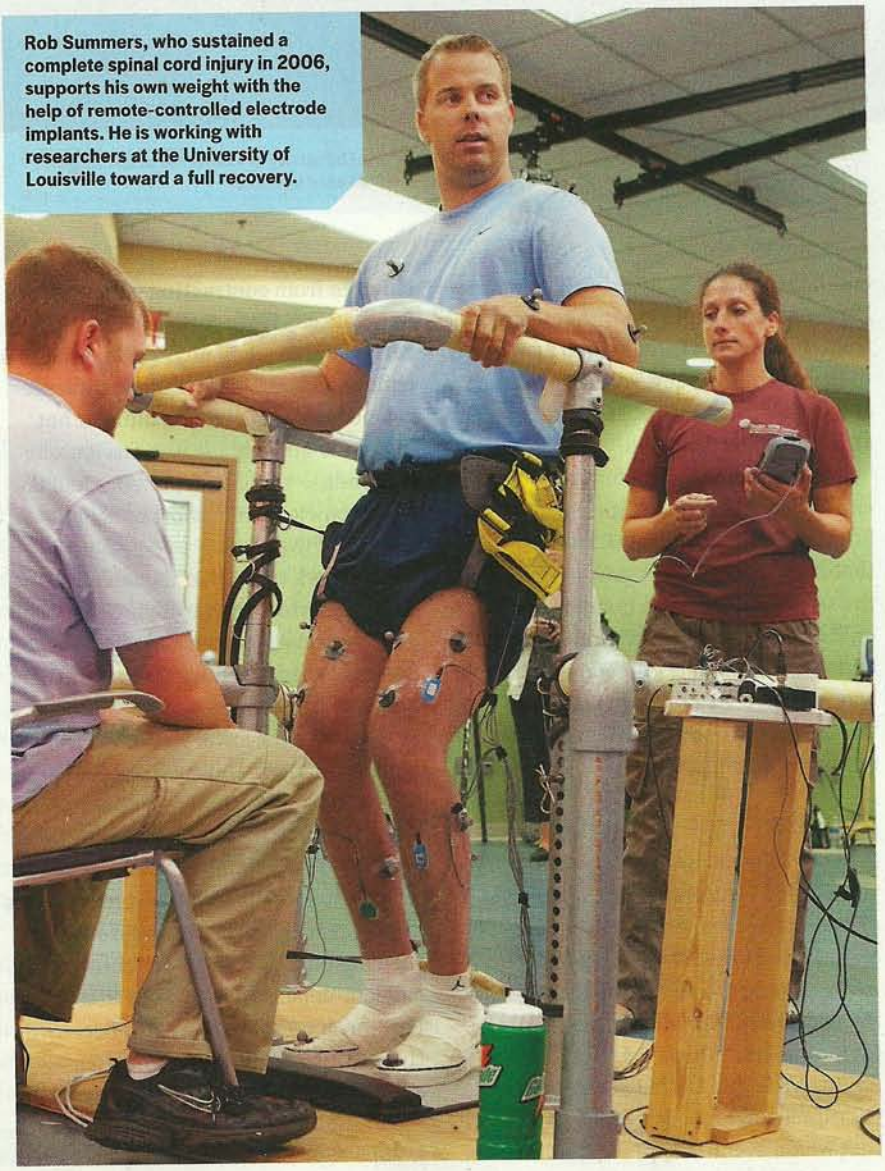
Standing Promise

by NATE BERG *additional reporting by* FANGFEI SHEN

ROB SUMMERS IS STANDING UP. Two feet on the ground, legs straight, hips squared. He has done it thousands of times before — out of bed in the morning to practice with his championship-winning collegiate baseball team, or up from the couch to get a snack. Most memorably, he stood up on a July night in 2006 to walk out the door and over to his parked car on a street in Portland, Ore. Standing next to his Ford Explorer, he saw the lights of another vehicle approaching from behind. It was coming fast — too fast.

Before he could get out of the way, the car threw him to the ground, and the driver fled what was a gruesome scene: Summers lay on the asphalt in a pool of blood, the victim of a hit-and-run that severed the connection between his brain and spinal cord and paralyzed him from the chest down.

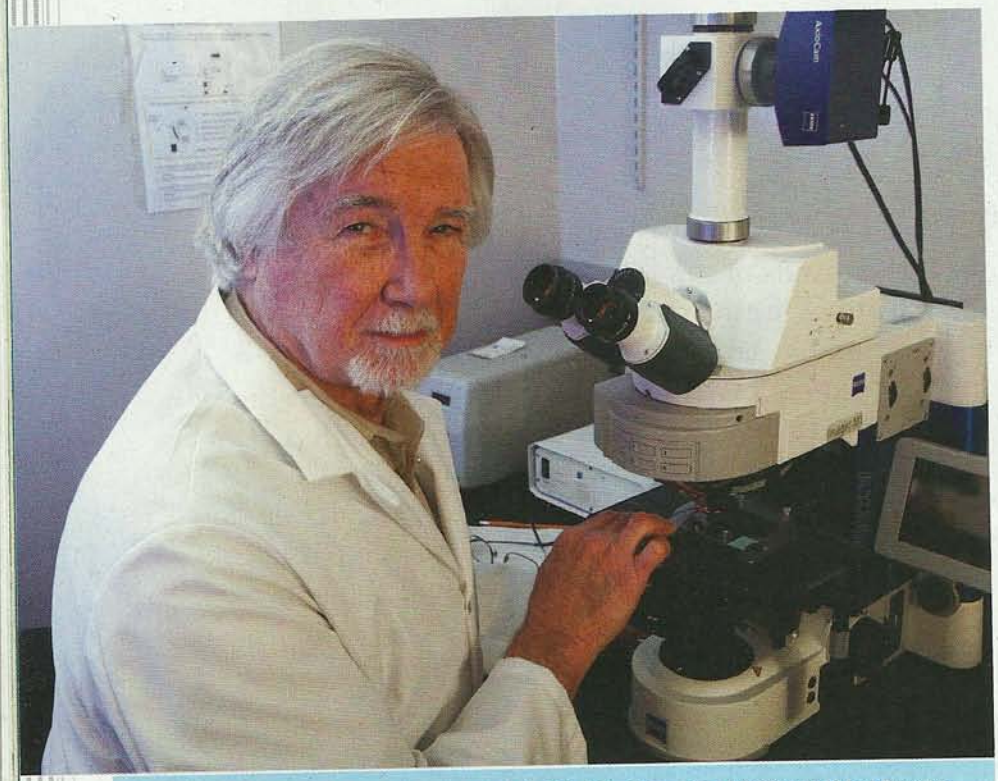
Fast-forward three and a half years: A 23-year-old Summers is standing up again. He's in a lab, hooked up to wires and sensors, and surrounded by doctors and research assistants. He is the first patient in an experiment that has gone fantastically right.



Rob Summers, who sustained a complete spinal cord injury in 2006, supports his own weight with the help of remote-controlled electrode implants. He is working with researchers at the University of Louisville toward a full recovery.

When Summers made it to his feet again, Reggie Edgerton, a neurobiologist at the University of California at Los Angeles, waited calmly nearby. As Edgerton had expected, the array of electrodes that researchers had implanted in Summers' lower back a few weeks prior was effectively reactivating Summers' limbs by restoring the natural connection between the muscles and the nervous system, which issues the commands for movement. With just a little electricity flowing into his lower spinal cord, Summers' leg muscles knew exactly how to get to work — without any input from the brain.

For years, scientists had assumed that the spinal cord was nothing more than a glorified telephone line carrying messages to and from the brain. The generally accepted wisdom was that the brain provided instructions for motion, from the voluntary "pick up the ball" to the involuntary "ouch, step off of that sharp tack." Cutting the telephonic spinal cord



Neurobiologist Reggie Edgerton works out of his lab at the University of California at Los Angeles to find ways to bring movement back to patients with spinal cord injuries.

out of the system by severing it completely, or even partially, meant that messages from the control center couldn't get down to the rest of the body. Paralysis was the end of that conversation; the puppeteer's strings had been clipped.

But over the course of four decades, and through dozens of experiments, Edgerton and his colleagues have shown that the spinal cord is smart in much the same way the brain is smart: It can, on its own, detect sensory information and send out signals that control the way we move. As Edgerton watched Summers stand straight, decades of research came into view.

MAKING CONNECTIONS

It was 1942 when Reggie Edgerton, age 2, was afflicted with infantile paralysis, a disease better known today as polio. It is a viral infection that takes up residence in the spinal cord and brain and attacks the neurons, or nerve cells, responsible for movement. In 1955, 13 years too late for Edgerton, the United States began the widespread use of a new polio vaccine that would eventually prevent millions of children from contracting polio and suffering its consequences. Today, Edgerton carries only a small physical trace of this childhood bout, in his slightly underdeveloped left arm. But it is difficult not to see the influence — unconscious, he contends — that the experience had on Edgerton's longtime effort to help the paralyzed walk.

That work took off in the mid-1970s, when Edgerton, then studying the way exercise impacts muscles, learned that Swedish scientists were tracing walking and standing motions directly to nerve signals from the lower spine. Spearheading the work was University of Gothenburg neuroscientist Sten Grillner, who ran chemical experiments on cats, the standard test animal for studying locomotion. Grillner had severed the cats' spines, rendering them paralyzed, and then injected them with an amino acid called L-dopa, routinely used to treat Parkinson's disease — a neurodegenerative disorder of the central nervous system characterized by motor symptoms. The exact mechanism behind the L-dopa signal is still not completely

Edgerton wondered: Could adults with complete spinal cord injuries train their spinal cords to learn to walk again?

understood, but one thing was clear: It was effective at getting the spinal cord to send chemical signals that stimulated the cats' otherwise immobile legs — and not just in a knee-jerk automatic response, but in more complicated steplike, rhythmic patterns. The motion, Grillner determined, was activated by the firing of interneurons — nerve cells that connect sensory neurons to motor neurons — in the lower spinal cord.

Edgerton took a six-month sabbatical in 1976 to study these interneurons with Grillner. Still working with cats on L-dopa, Grillner and Edgerton probed the animals' spinal cords with a small glass electrode. It was meticulous work, but measurements of electrical activity eventually allowed the scientists to map the locations of some of the specific interneurons that were telling paralyzed leg muscles to move.

In another set of studies, the Grillner team severed the spinal cords of kittens shortly after birth. Yet with time and training, the kittens were able to walk again on treadmills, without any L-dopa or electrode stimulation at all. Moving the kittens through repeated stepping motions seemed to help them regain movement. "If the injury occurs early after the birth, there's a much greater chance of recovery," explains Edgerton. The neonatal nervous system has some unique abilities to repair."

That made him wonder: Would adults with complete spinal injuries, whose bodies heal less readily, ever be able to recover? Would it still be possible to train their spinal cords to learn how to walk again? "When I came back to UCLA," Edgerton says, "I wanted to focus on this issue completely."

BOTH IMAGES: RENE MACURA

In 1978, back in his lab at UCLA, Edgerton began a series of experiments on adult cats whose spinal cords were severed. With their torsos slumped into tiny vests attached to a bar, the paralyzed cats were positioned with their hind paws on a treadmill. With the treadmill turned on, the cats' hind legs went trotting along. Remarkably, the motor neurons still knew how to send walking orders to the legs. Edgerton concluded that the sensory signal to walk was coming from weight on the paws, instead of from the brain.

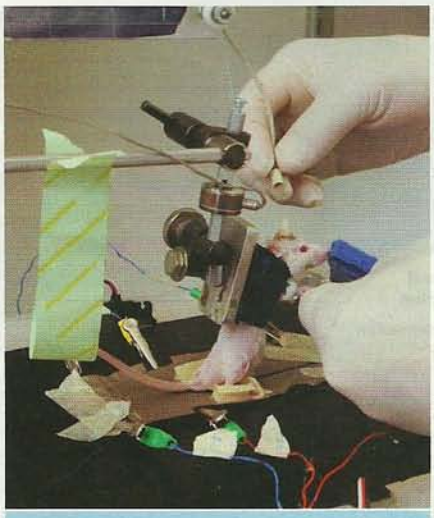
Others in the field chalked up these results to reflexes, much like the involuntary motion that occurs when a doctor taps your knee. But by the late 1980s, advanced pharmacology allowed Edgerton to prove them wrong: To do so, he injected paralyzed cats with strychnine, a toxin commonly used in rat poison. Strychnine blocks glycine, an amino acid that inhibits nerve function in the brain stem and the spinal cord. With the glycine shield gone, neural activity went up. Within half an hour, cats that had been paralyzed for three months began walking as if their spinal cords were intact — this was hardly a reflex effect.

"We showed that a spinal cord could learn if you expose it to a training paradigm," says Edgerton. "The training provides stimulus. If you stop training it, it forgets how to step."

By the early 1990s, Edgerton and his team decided to see if they could teach the human spinal cord some lessons as well. Their subjects were patients with partial and complete spinal cord injuries. Only those with partial injuries showed improvement with physical therapy, including regular assisted walking and guided leg exercises on the treadmill. Many ultimately regained voluntary control of their leg muscles, standing up and even walking on their own. The exercise, researchers presumed, rebuilt the connection between the brain and the spinal cord, awakening, or even regrowing, the locomotive neural circuits the injured patient had lost.

WIRED FOR MOVEMENT

Edgerton wanted to train the spinal cords of his completely paralyzed patients, too. He knew they needed something more than just physical therapy. Perhaps direct electrical stimulation of the spinal cord, he conjectured, would do what mere physical therapy could not.



A UCLA graduate student working with Reggie Edgerton conducts electrode experiments on a rat whose spine is severed.

To test the idea, he severed the spinal cords of red-eyed, white-furred lab rats, leaving them paralyzed from their hind legs down. Then his team attached tiny electrodes to a spot a few vertebrae higher than the tail, on top of membranes just above the spinal cord. The wired rats were placed in vest-like harnesses over a treadmill and, through a system of wires and controllers connected to the electrodes, zapped with electrical current.

The strategy worked: With the right frequency of electricity (usually 40 hertz), the electrodes could stimulate the legs of paralyzed rats to walk as if their spinal cords had never been sliced in half. "With enough training, the rats could step forward, backward and sideways at a range of speeds," Edgerton explains. The stepping movements stopped once the electrodes were turned off, the hind legs of these paralyzed rats dragging once more on the moving treadmill. Over time, with rigorous training, the rats were able to walk again as long as the electrodes were turned on.

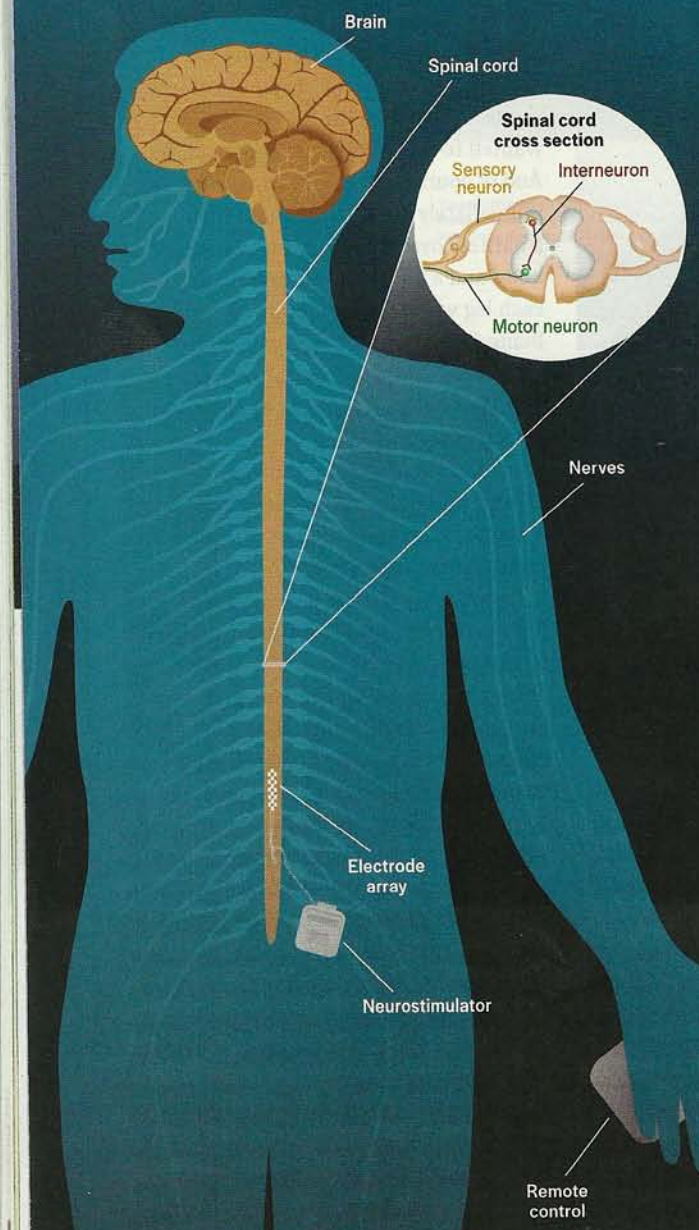
Bolstered by the success of his experiment, Edgerton felt he might be ready to use electrode implants to help humans as well. At the time, Edgerton was also serving on the board of what was to become the Christopher and Dana Reeve Foundation, the paralysis research and aid group of the late *Superman* actor who was paralyzed from the neck down after a horse-riding accident in 1995.

In 2000, Reeve heard about Edgerton's effort to retrain the spine to walk, and he expressed interest in visiting his lab. Edgerton and his team showed Reeve some of the treadmill and electrode work they were doing with rats, cats and humans. "And then we asked him if he wanted to try standing on the treadmill. And of course he did," says Edgerton. "He immediately became a big fan." There was a harness over the treadmill to support his body, and a physical therapist controlled each leg while the treadmill was moving. Being in an upright position, Edgerton says, "was kind of an exciting time for him." Seeing the promising electrode work in rats impressed Reeve, too. In the years after the visit, his foundation granted about $4 million to Edgerton's lab to find a way to train human patients with complete spinal cord injuries to walk again.

Reeve, who died in 2004, would have been thrilled to see the progress made by one of Edgerton's former postdocs, neuroscientist Susan Harkema. Harkema does much of her work at the University of Louisville in Kentucky, where she has been developing human treatments for complete spinal cord injuries, using the same electrode stimulation and surgical strategy Edgerton used with red-eyed rats.

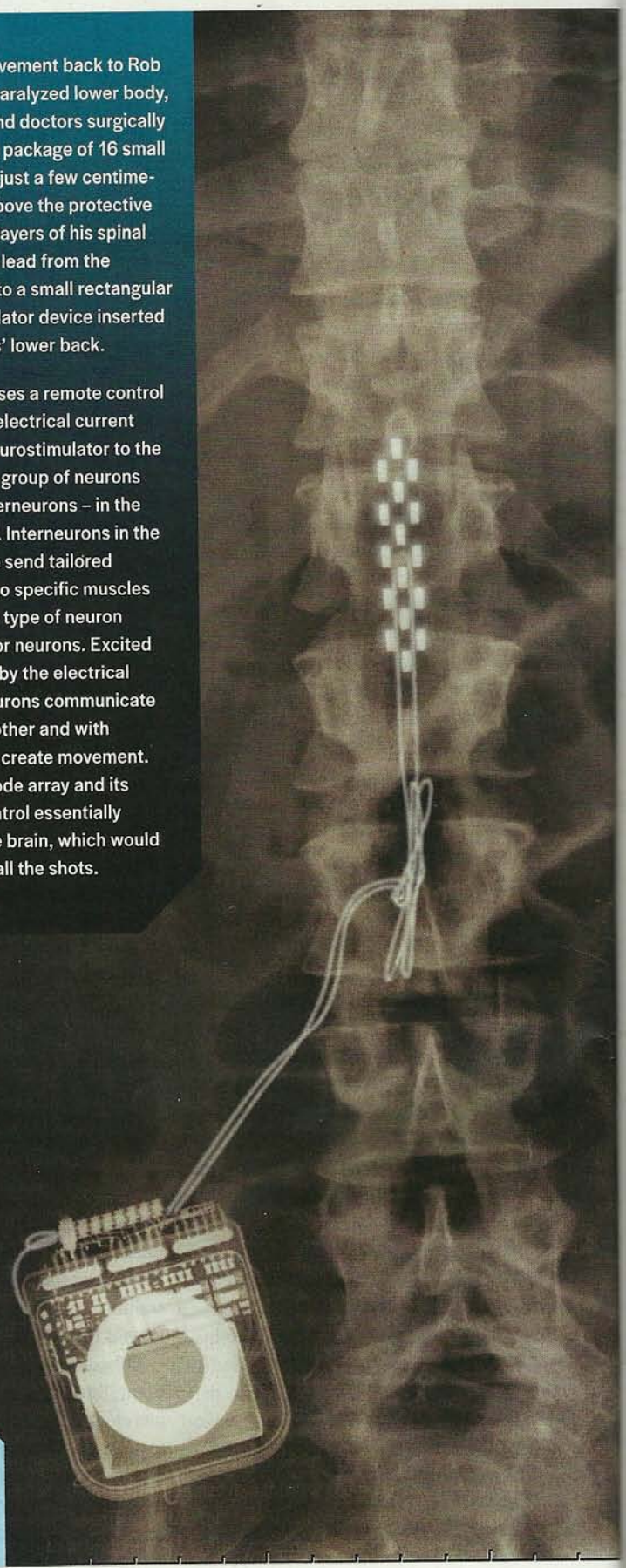
With the intention of delivering electricity directly to a human spine, Harkema repurposed a medical device that was originally designed to suppress pain. The device, consisting of 16 electrodes packaged in a tiny array a few centimeters long, would be surgically implanted into a patient's lower back, just over the dura — the outermost of three layers of membranes surrounding the spinal cord. Wires would lead from the array to a small, rectangular neurostimulator device that packed a charge. This would be implanted beneath the skin in the lower back. Just as Edgerton's device activated the rats' nervous systems, Harkema's rechargeable and programmable device would tell the electrodes connected to the dura how much electricity to apply to neurons in the lower spinal cord, and how often. Once those neurons fired, they would remember how to communicate with each other, and with muscles as well. Over time and with

The Body Electric



To bring movement back to Rob Summers' paralyzed lower body, scientists and doctors surgically implanted a package of 16 small electrodes, just a few centimeters long, above the protective membrane layers of his spinal cord. Wires lead from the electrodes to a small rectangular neurostimulator device inserted in Summers' lower back.

Summers uses a remote control to send an electrical current from the neurostimulator to the array and a group of neurons – called interneurons – in the spinal cord. Interneurons in the lower spine send tailored messages to specific muscles via another type of neuron called motor neurons. Excited into action by the electrical charge, neurons communicate with each other and with muscles to create movement. The electrode array and its remote control essentially replace the brain, which would normally call the shots.



A post-operation fluoroscopy shows an electrode array and neurostimulator implanted in Rob Summers.

training, patients who had lost a connection between the spinal cord and the brain would use a remote control to communicate conscious instructions to the device.

But before this technique could advance, Edgerton and Harkema needed a patient and FDA approval.

OFF THE BENCH

After his injury, Summers, still a ballplayer at heart, started doing his own research to find a spinal cord therapy program that emphasized exercise-based training. In 2007, he met Harkema and moved to Louisville.

By 2009, Edgerton's work had shown enough promise for the FDA to approve his and Harkema's request to do a set of human experiments with the electrode device. The test subjects would need to have a completely severed spinal cord, with no motor activity below the waist. And they would need to be able to perform many long and potentially grueling physical experiments to try to replicate the success Edgerton saw in his rats. The subjects would have to spend hours on the treadmill, just to make sure there was no chance of recovery with physical training alone. The rigor involved would require someone with both strength and perseverance. Summers, the former college athlete, was a perfect fit.

Harkema and her team first worked with Summers on locomotor training, without electrical stimulation. As expected, there was no improvement in Summers' ability to stand or move below the level of his spinal cord injury.

In late 2009, Harkema and Edgerton's team implanted the electrode array directly over Summers' dura. The neurostimulator device and remote-controlled mechanism still bulge out like a small stack of business cards on the lower right side of his back.

A few weeks after recovering from the surgery, Summers arrived in the lab, expecting a long process of fits and starts. But on just his first attempt to stand, the electrode array got Summers' neurons talking. A researcher turned on the neurostimulator. Strapped into a harness and attached to sensors, Summers was lowered over a treadmill. As his feet touched down and his lower body started to feel his weight, Summers' legs engaged — just as the rats' legs did in Edgerton's earlier treadmill experiments. The trainers stabilized Summers during this process, but as he stood upright on the treadmill, they slowly took their hands off him, until he was standing alone. "Everyone was in shock," Edgerton recalls.

> Slowly and jerkily, Summers' body started to regrasp very basic but astounding control.

Summers was standing upright, carrying a third of his own weight on two legs, the interneurons in his spinal cord now electrically stimulated, shouting directives to his motor neurons and muscles to stand straight. Slowly and jerkily, Summers' body started to regrasp very basic but astounding control.

With the electrode array turned on, the spinal cord was awakened. It could receive and process sensory information again. With the help of the electrodes, it could sense that there was pressure on the soles of Summers' feet, and it could react. As it awoke, Summers' spinal cord became more and more perceptive. Summers was consciously creating the preconditions for his body to stand, by weighting his feet, but he wasn't consciously doing the standing. Edgerton calls it "indirectly voluntary" and notes that this combination of conscious and automatic activity is shaking up the way researchers think about movement.

After a few months of training with the implant, Summers began to show notable improvement in his ability to stand more stably, for longer periods of time. Unexpectedly, he also regained other types of movement below the waist: wiggling his toes, moving his ankles, bending his knees and flexing his hips. The more his motor neurons communicated with the muscles in his lower body, the more he remembered how to move. The training was augmented by the electrical stimulation itself. Edgerton says the current might have reactivated damaged neurons or caused new neurons to grow across the site of the injury, or both. Although he could stand only a few minutes in a harness that first time in 2009, Summers now practices unassisted for an hour a day. He regularly does cardio and weight training as well.

Susan Harkema, Rob Summers and Reggie Edgerton speak at a Christopher and Dana Reeve Foundation event in 2011 in New York.

Before this treatment, Summers, like most people with spinal cord injuries, could not sweat below the level of his injury, and he had trouble regulating his blood pressure and getting an erection; he had no control over his bladder and bowels. "I had a prescription list close to two pages long" to regulate most of those functions, he says. But after the implant and through his extensive training, Summers has regained control of most of these functions and has ditched the drugs — an unexpected result that he says has given him back much of the freedom he lost after his accident.

Edgerton can't say for sure why those functions returned, although he hypothesizes that they may have come back once more blood was pumping into the legs as the muscles started to engage again. This caused the body to remember and restart the lost functions. "This experiment demonstrates that it can happen. That's the key. And so the question is how many patients will be able to benefit how much? That's where the research needs to go."

The electrode device used on Summers is not fine-tuned enough for walking, a

Scientists Set Their Sights on a Cure

Electrical stimulation is one way to get paralyzed patients back on their feet, but researchers are also testing a number of other novel methods in hopes of finding a pure biological cure – one that transcends invasive intervention or constant mechanical support. The strategies below are preliminary but promising.

Preventing damage

After a spinal cord injury, nearby neurons lose insulation and the ability to communicate via natural electrical impulses. When scientists gave mice an oral drug called **LM11A-31** (designed to prevent neural degeneration in Alzheimer's patients) just hours after a complete spinal cord injury, it limited the death of cells that protect nerve fibers, allowing test rodents to retain their ability to walk and swim. The drug binds with proteins that normally kill off the protective cells after an injury; with the proteins disabled, more neural connections may remain intact, says Sung Ok Yoon, lead author of a study published this January in the *Journal of Neuroscience*. LM11A-31 is noninvasive, low risk and FDA-approved, but researchers have yet to try it on people with paralysis. ***Caveat:*** *The drug is not yet tested in humans for paralysis treatment, and it must be delivered right after the injury, or it won't work.*

Repairing nerve cells

By reinsulating damaged nerves and regenerating nerve cells, **Schwann cell transplants** have earned their stripes in paralyzed mouse, pig and primate studies over the past decade. In healthy individuals, Schwann cells wrap themselves around nerve fibers to insulate and protect them, much like the coating on a household electrical cord. When transplanted to the site of a spinal injury, the cells can bridge the gap in the spinal cord and pump out growth chemicals to induce new nerve fibers to sprout, according to neurologist Kim Anderson, a researcher at the Miami Project to Cure Paralysis. During an early clinical trial at the Miami Project last year, researchers took Schwann cells from an easily accessible sensory nerve in a patient's leg, grew them in culture and injected them at the point of the spinal cord injury. Results will be available in about a year. Another kind of protective cell, meanwhile, offers an alternative method of repair, as described in a study published in the journal *Brain*. In that work, scientists removed **olfactory ensheathing cells** from the noses of dogs with complete spinal cord injuries, and injected them at the site of the severed nerves. The result was improved movement and coordination between fore and hind legs. ***Caveat:*** *To date, this strategy has only been able to allow better communication between nerve cells in the spinal cord, but there is no evidence of improved communication between those neurons and the brain.*

Restoring function

To encourage nerve growth over longer distances, researchers are looking to **stem cells**. A study published in *Cell* last year demonstrated that human and rat stem cells could be grafted onto the spinal cord of paralyzed rats, forming new nerves capable of communicating across the injury site. The result? Movement in every joint in the rats' hind legs. Now a clinical trial in Zurich provides the first evidence that stem cell therapy can restore some function in people with complete spinal cord injuries. Twelve months after being injected with brain-derived stem cells near the injury site, one of the three human participants has regained some feeling in the lowest portions of his spine. Researchers don't know exactly how the stem cells work, but they assume they are performing nerve repair. "It's probably more than one type of action," said neurosurgeon Stephen Huhn, who leads the Central Nervous System program at StemCells, the company that sponsored the study. ***Caveat:*** *Stem cell transplants to the central nervous system remain highly experimental.* BREANNA DRAXLER

much more complicated movement. Edgerton and Harkema are now working on a more sophisticated stimulator that could help patients take the next step. The new device will have electrodes like the ones implanted in Summers, but the stimulation patterns will be more complex, allowing for varied intensity and more targeted stimulation. They have a design and now need the resources to build, test and get it FDA-approved for human trials.

ROUNDING THE BASES

Summers sees himself walking in the near future, and maybe even swinging a bat again. After a stint in Los Angeles, where he was working on a documentary about his life, he is back in Louisville to continue with therapy. He has also started the Rob Summers Fund, which is under the umbrella of the Reeve Foundation, to help raise money for finding a cure for paralysis.

For his part, Edgerton is cautious about saying that he's found a cure or that this treatment will get spinal injury patients out of their chairs and strolling down the street. But, at the core, that's the motive behind this work — and behind the decades Edgerton has spent getting to this point. He and Harkema's team have already implanted electrodes in three other human subjects, who wish to remain anonymous. And his team has FDA approval to work with two more patients. The second, third and fourth patients, following in Summers' footsteps, are already standing and gaining control of bodily functions. "We're highly encouraged," Edgerton says.

And he's got no plans for getting out of the game, even as he approaches his 73rd birthday. Edgerton says this is one of the most exciting times of his career. "What has happened over the years is the spinal cord keeps surprising," he says. As it does, Edgerton and others in his field are likely to get better at harnessing its ability and making dramatic improvements in patients' lives.

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