

FIRST STEPS TO A REVOLUTION

Blockbuster studies of electrical stimulators promised huge advances for people with spinal-cord injuries. Now comes the hard part — making it a reality.

BY CASSANDRA WILLYARD

Rob Summers was flat on his back at a rehabilitation institute in Kentucky when he realized he could wiggle his big toe. Up, down, up, down. This was new — something he hadn't been able to do since a hit-and-run driver left him paralysed from the chest down. When that happened four years earlier, doctors had told him that he would never move his lower body again. Now he was part of a pioneering experiment to test the power of electrical stimulation in people with spinal-cord injuries.

"Susie, look, I can wiggle my toe," Summers said.

Susan Harkema, a neurophysiologist at the University of Louisville in Kentucky, sat nearby, absorbed in the data on her computer. She was incredulous. Summers's toe might be moving, but he was not in control. Of that she was sure. Still, she decided to humour him. She asked him to close his eyes and move his right toe up, then down, and then up. She moved on to the left toe. He performed perfectly.

"Holy shit," Harkema said. She was paying attention now.

"How is that happening?" he asked.

"I have no idea," she replied.

Summers had been a university baseball player with major-league ambitions before the vehicle that struck him snapped all the ligaments and tendons in his neck, allowing one of his vertebra to pound the delicate nerve tissue it was meant to protect. Doctors classified the injury as complete; the motor connections to his legs had been wiped out.

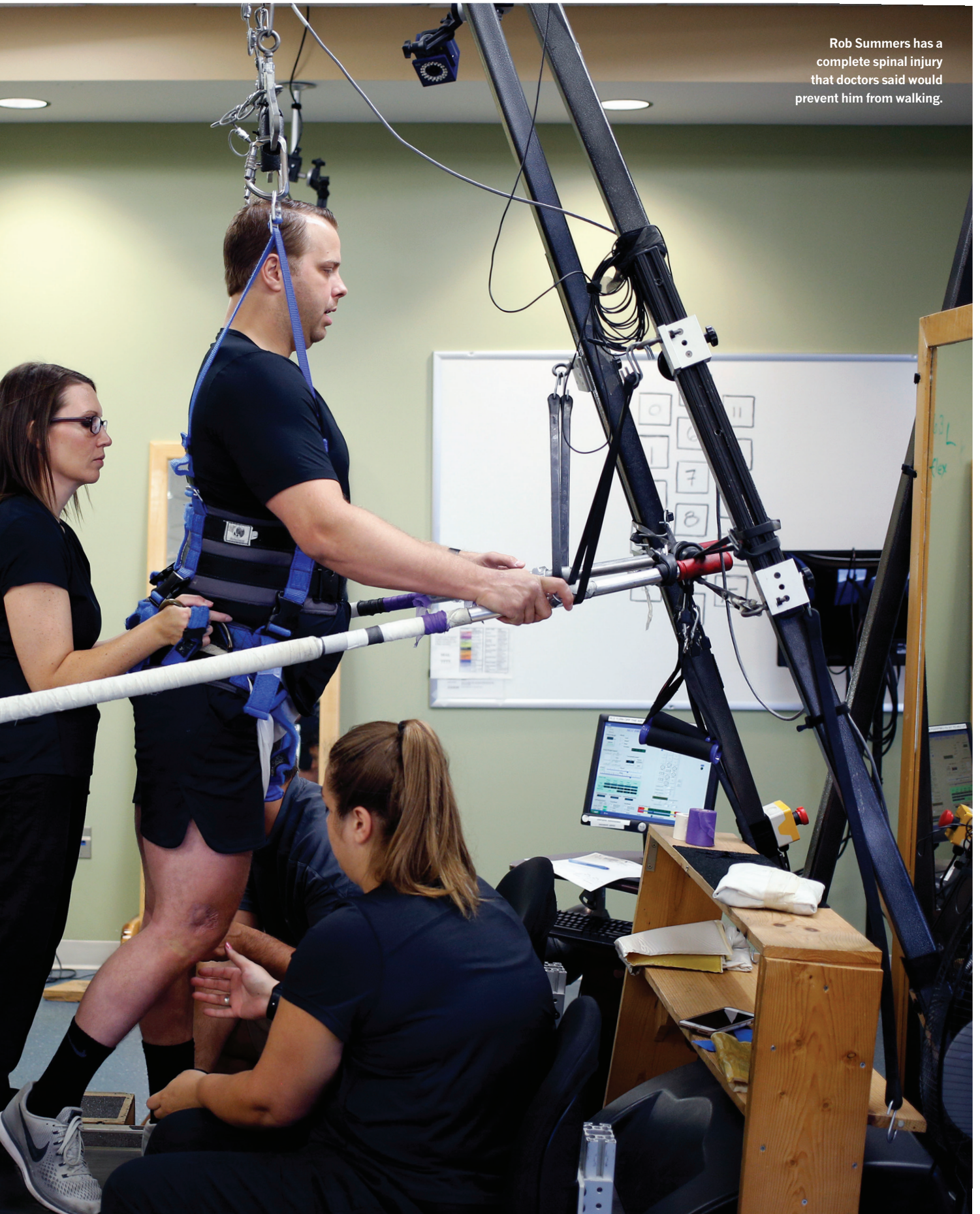
When Harkema and her colleagues implanted a strip of tiny electrodes in his spine in 2009, they weren't trying to restore Summers's ability to move on his own. Instead, the researchers were hoping to demonstrate that the spine contains all the circuitry necessary for the body to stand and to step. They reasoned that such an approach might allow people with spinal-cord injuries to stand and walk, using electrical stimulation to replace the signals that once came from the brain.

So, when Summers intentionally moved his toes, Harkema was dumbfounded.

Prevailing wisdom has long held that spinal-cord injuries represent severed connections between the brain and the extremities. For decades,



Rob Summers has a complete spinal injury that doctors said would prevent him from walking.



researchers have focused on repairing those connections, for example with stem cells. But findings from Harkema's group and other laboratories suggest that some connections remain intact, even for people with the most severe damage. Electrical stimulation seems to help to amplify the messages being sent across the injury, and to re-establish these links.

The surprise awakening of Summers's nerve connections is part of a string of advances that has invigorated research into spinal-cord injuries. Last year, labs in Kentucky, Minnesota and Switzerland made headlines with a spate of case studies. Stimulators that were originally designed to treat chronic pain have now helped about a dozen people with paralysis to wiggle their toes, flex their legs or walk with support — for up to 1 kilometre in some instances. But the devices also seem to offer broader benefits. Some study participants saw improvements in blood pressure, bowel and bladder control and sexual function — abilities that people with spinal-cord injuries often value more than the use of their legs. In some cases, these benefits persisted even after the stimulators were turned off. The results have bolstered hopes for an improved quality of life, even for people who were paralysed years or decades ago, and the findings are upending conventional wisdom about spinal-cord injuries. “This is a new ball game,” says Reggie Edgerton, a physiologist at the University of California, Los Angeles (UCLA), who has been closely involved with the work.

The waiting lists to get into stimulation trials are now thousands of names long. And at least one hospital has begun offering the experimental procedure — at a cost of tens of thousands of dollars — without formal approval or a full reckoning of the risks and benefits involved.

To some, the hype sounds familiar. The quest to cure paralysis has cost hundreds of millions of dollars and has so far resulted in little more than bold predictions and dashed hopes. Actor Christopher Reeve, one of the most recognizable public faces of spinal-cord injury, firmly believed he would walk again thanks to the burgeoning field of stem cells. “I know there's a cure coming for the kind of injury that I have,” Reeve said in a 2001 interview, three years before he died. But nearly two decades later, that long-promised cure has yet to materialize.

The field is at a crucial juncture as it determines how to translate miraculous-sounding results into a workable therapy, says Keith Tansey, a neurologist at the Methodist Rehabilitation Center in Jackson, Mississippi. Researchers still don't entirely understand how stimulation works. “We've got to learn more about this,” he says. “We've got to worry less about whether we looked good on the cover of *TIME* magazine and more about whether we're really going to move towards helping patients.”

A PATTERN FOR PROGRESS

The path to Summers's toe wiggle began with cats on treadmills.

In the 1970s, Edgerton started working with a long-studied model for understanding locomotion. Cats that have had their spinal cord severed can be suspended over a treadmill and trained to walk again by simply guiding their legs in a step-like motion. With practice, the animals will adjust their gaits to match the speed of the treadmill and even switch directions — with no input from the brain required. The spinal circuitry propelling them forward, called a ‘central pattern generator,’ controls the movements, and Edgerton was trying to understand how it worked.

In 1993, when Harkema joined Edgerton's lab, she wasn't all that interested in the spine — she says that she chose UCLA for the weather. But as Harkema began working with the cats, she became fascinated by how the animals regained so much function. Edgerton tasked Harkema with setting up a similar experiment in humans who had spinal-cord injuries. Perhaps regimented training designed to awaken a central pattern generator would allow them to walk, too.

It worked to some extent. Step training on the treadmill with body-weight support helped people with spinal-cord injuries, especially less severe injuries, improve their ability to move. But Harkema and Edgerton wanted to see a bigger effect. Epidural stimulators, which deliver current to the lower part of the spinal cord, seemed like a good option.

The devices have been used to treat chronic pain since the 1960s. But researchers had seen evidence early on that they could do more. In people with spinal-cord injuries, for example, the stimulators seemed

to reduce the rate of involuntary spasms. In one study¹, researchers examined people with spinal-cord injuries who had been implanted with stimulators for this reason. When scientists turned up the stimulation, participants began moving their legs rhythmically and automatically. “It was — still is — probably the most direct evidence for a so-called central pattern generator for locomotion in humans,” says Karen Minassian, a medical physicist at the Medical University of Vienna. There were even hints from a case study² that stimulation could restore the ability to move voluntarily, at least in people with incomplete injuries: those who had retained some sensation and movement in their lower bodies.

In 2002, researchers in Arizona reported suspending a 43-year-old man with a spinal injury over a moving treadmill while stimulating his spine³. He also had an incomplete injury. After training and stimulation, he was able to walk with “a near-effortless, coordinated locomotion pattern”, according to the authors.

Harkema and Edgerton began discussing the possibility of using the same approach. They just needed a test patient to prove the principle. Summers was determined to be their guy.

STANDING DELIVERED

During the summer of 2006, Rob Summers was living and breathing baseball. A pitcher for the Oregon State University Beavers, he had just missed playing in the College World Series championship because of a hip injury. So he was training hard to secure a starting position for the upcoming season. One night, as he retrieved a gym bag from his car, he heard a vehicle speeding down the street. He caught just a glimpse of the headlights before it struck him and sped off. Summers lay on the ground bleeding until early the next morning, when a neighbour found him.

Summers doesn't recall much about the month he spent in hospital, but he does remember that the doctors waited until he was surrounded by family to tell him he was paralysed. They didn't mince words: “You're never going to walk. You're never going to feel anything.” Summers refused to believe it. The doctors didn't know how stubborn he was, how hard he could work. “I'm going to beat this,” he told his parents.

After a year of intense rehab, Summers had regained some sensation in his limbs, but he still couldn't move his lower body: his injury was considered ‘motor complete.’ Yet Summers was convinced he just needed the right therapy. So, he and his parents sent out more than 200 e-mails to research facilities around the world — “Israel, Europe, Russia, Cuba, Japan, China, South America, you name it,” Summers says.

The letter-writing campaign led him to a rehabilitation training workshop in Texas, where he met Harkema. By then, she had launched her own lab at the University of Louisville. In September 2007, Summers flew there with his dad to tour the facility. When Harkema mentioned that her team had plans to look at epidural stimulation, Summers was stoked. He was supposed to fly back to Portland the next day, but instead he rented an apartment and called Harkema. “I'm in,” he said. “I'll see you tomorrow at 8 a.m.”

In Louisville, Summers underwent more than two years of intensive rehab to assess whether he had any capacity for recovery without stimulation. Then, in December 2009, Harkema's team fitted him with an epidural stimulator. They placed a 16-electrode array in the space between his vertebrae and his spinal cord. A wire connected the array to the stimulator, a rechargeable device about half the size of a deck of cards, which sits just above his buttocks. Doctors controlled the stimulator remotely.

When the researchers turned the stimulator on, Summers immediately felt a tingling sensation. Three days later, the team tried to get him to stand. Initially, a harness supported all of his weight. The team gradually began to reduce that assistance until Summers was standing independently. He looked at his leg muscles contracting in the mirror. “That can't be real,” he thought. Then he looked around the room. His mother was in tears. “People were crying and yelling and asking me ‘how is this happening?’” Harkema says. “It was a little pandemonium.”

Still, that was nothing compared with the commotion that erupted six months later, when electrical stimulation allowed Summers to wiggle his toes. Harkema's team hoped to kick-start the circuitry required for standing and stepping in the spine and legs, but they weren't expecting



Sebastian Tobler (centre) steps with the aid of researcher Grégoire Courtine (right) and neurosurgeon Jocelyne Bloch.

to get any help from the brain. Harkema called Edgerton at his lab in Los Angeles to tell him about Summers's toes. "Oh God, this can't be true," Edgerton remembers thinking. "Everybody's going to think we're quacks."

STEPS TAKEN

When Harkema and her colleagues published the details of Summers's case⁴ in 2011, many scientists were sceptical. "I did not believe it," says Kendall Lee, a neurosurgeon at Mayo Clinic in Rochester, Minnesota. Everything Lee had been taught told him that once connections to the brain are lost, they don't come back.

But, gradually, the evidence began to mount. Harkema and her team published another study⁵ in 2014 involving Summers and three more people, including two who'd had no movement or sensation in their lower bodies. All regained some voluntary movement. Soon, others were trying the approach in humans, and looking to see whether it could allow trial participants to take steps off the treadmill.

Grégoire Courtine, a neuroscientist at the Swiss Federal Institute of Technology in Lausanne (EPFL), had also studied with Edgerton, starting at UCLA a couple of years before Harkema left for Louisville. He moved to Europe in 2008 to study epidural stimulation in rodents, and eventually in rhesus macaques.

By 2015, Courtine felt ready to test the technology in humans. His team used the same off-the-shelf pain stimulator Harkema had used, but tweaked the software so that the device could deliver patterns of stimulation timed to coincide with the act of walking. "We really try to activate the spinal cord as the brain is trained to do," Courtine says. And there was another major difference from Harkema's studies: Courtine's team recruited people with incomplete injuries, hoping that it might be easier to show recovery in this group than in people with complete injuries.

Meanwhile, Edgerton helped a third group, at Mayo Clinic, get another trial under way. In 2016, Lee, rehabilitation scientist Kristin Zhao and their colleagues set out to replicate Harkema's results. They recruited two participants who did nearly six months of physical therapy before being implanted with the stimulator, and then another ten months with the stimulator turned on. The aim was to show that stimulation and training

could improve their ability to stand and move their lower bodies voluntarily. But the first participant achieved those goals so quickly that the researchers decided to add walking to the protocol.

In autumn 2018, the three teams published results on the first eight trial participants⁶⁻⁸. All told, six managed some form of walking across the ground with assistance such as harnesses, crutches or parallel bars. The other two experienced benefits, too: with stimulation, they managed to sit and stand independently, and one could take some steps on a treadmill with support.

"It was really just this past year that the critical mass built up," says Chet Moritz, a rehabilitation medicine researcher at the University of Washington in Seattle. "That's really where it started to feel like a breakthrough."

HOPES AWAKEN

The field has seen 'breakthroughs' before, though. Reeve argued passionately and convincingly to fund stem-cell research in the hope of repairing nerve damage. Videos have shown paralysed rats whose spines had been injected with cells miraculously regaining the ability to walk or use their paws. A cure has often seemed close at hand.

Replicating those results in people has proved difficult, however. Although there are ongoing human trials with stem cells, some of which show promising results, excitement for the approach — from funders, patients and researchers — has dwindled, says Tansey. Other high-tech approaches to reversing paralysis, such as brain-machine interfaces, are still being developed. Powered exoskeletons are already on the market, but they're expensive. And they don't address the underlying problem of restoring neural connections. "We've all heard 'five years down the road there's going to be a magic pill' or whatever," says Peter Grah, a neuroscientist at Mayo Clinic who was a joint first author on the stimulation study⁶ and who has a spinal-cord injury himself. "That's what you hear all the time, because five years is long enough that everyone forgets."

But to a lot of interested onlookers, stimulation shows promise that goes beyond the hype. In particular, it already has a long history in treating chronic pain, says Matthew Rodreick, executive director of Unite 2 Fight Paralysis, a spinal-cord-injury advocacy group based in

Hood River, Oregon. “This is a device that’s on the market and has been implanted in hundreds of thousands of people,” he says. That doesn’t mean the strategy will succeed, but at least the path to approval has been cleared, he says.

There are still major questions as to how stimulation works and why some benefits seem to persist after the stimulators are turned off. It is becoming clearer that, for many individuals with injuries considered complete, some neural pathways for motor control from the brain do survive. They’re just dormant and cannot elicit a response in the neurons below the site of the injury. Epidural stimulation seems to make neurons more excitable — more likely to fire when confronted with signals from the brain telling them to move a toe or to start walking. Electrical current can force neurons to fire and muscles to contract, but that’s not what’s happening for those who have begun to walk. “The person doesn’t have to step,” Moritz says. “It’s not robotic.”

As for why some benefits persist in some participants, there are a couple of possible explanations. Stimulation might allow the individuals to participate more fully in rehabilitation, strengthening muscle and nerve connections through exercise. Or it might promote plasticity, which helps to rewire the circuits around the injury. That’s a particularly tantalizing possibility, because it could mean that there’s potential for improvement over time.

Still, researchers have yet to work out who might benefit most from the procedure. Harkema says that all 20 people who have been implanted in Louisville have regained some voluntary movement. But to Tansey, it seems clear that not everyone with a spinal-cord injury will improve. He wants to see a way to screen individuals — because implanting a medical device inside the spine is no trivial matter. There are risks.

Although the stimulators are approved by the US Food and Drug Administration to treat chronic pain, they do occasionally cause unwanted, even dangerous, side effects. Recipients report that they have been shocked, been burnt or suffered nerve damage that led to muscle weakness or even paralysis. A 2018 investigation by the Associated Press found that stimulators have garnered almost 80,000 injury reports since 2008 — more than for any other medical device, apart from insulin pumps and metal hip replacements.

And there might be risks that are specific to individuals with spinal-cord injuries, who are more susceptible to infections, and often have low bone density. One participant in the latest study from Harkema’s team⁸ broke their hip, which required multiple surgeries that led to an infection.

There have also been some reported problems that are difficult to explain. In 2015, Xander Mozejewski, who has a spinal-cord injury, joined one of Edgerton’s trials to test the effect of non-invasive ‘transcutaneous’ stimulation, in which electrodes are placed on the surface of the skin. He later began experiencing spasms and pain in his lower body that grew steadily worse. In 2016, doctors implanted an epidural stimulator to try to control the spasms, but the device seemed to make things worse, and Mozejewski eventually had it removed. In 2018, he filed a medical malpractice suit against UCLA, Edgerton, NeuroRecovery Technologies — the company in San Juan Capistrano, California, that Edgerton co-founded — and others. The case is ongoing, but in a statement to *Nature*, Nick Terrafranca, chief executive of NeuroRecovery Technologies, said: “The stimulator has been used with over 60 study participants with no adverse event reported that was directly related to use of the device developed and provided by the company.” Terrafranca adds that side effects the company recorded, including muscle spasms, “were transient in nature.”

Harkema’s research has also garnered some criticism. In 2015, one of her colleagues sent letters to the University of Louisville’s Institutional Review Board, its Human Subjects Protection Program and the National Institute on Disability, Independent Living and Rehabilitation Research (NIDILRR), which funded some of her work, expressing concern over

four of Harkema’s studies. An internal investigation revealed that the scientists had failed to track and monitor adverse events, had deviated from study protocols and had misplaced records. As a result, the NIDILRR defunded one of the studies, a \$914,000 investigation into the effects of a muscle relaxer and treadmill training on people with spinal-cord injuries. The US Office for Human Research Protections also conducted an investigation, but did not impose sanctions on Harkema. The agency also said that corrective actions taken by Harkema’s team had adequately addressed the non-compliance.

Harkema acknowledges that her team wasn’t keeping records perfectly, but she denies all allegations of serious wrongdoing, especially the accusation that her team put patients at risk. “Anyone who visits our research programme is actually astonished by all of the things that we put in place in order to protect our research participants,” she says.

Her research has continued apace. The Christopher & Dana Reeve Foundation in Short Hills, New Jersey, is supporting work to test epidural stimulation in 36 more individuals at the lab in Louisville. As of July, 11 people had been implanted with stimulators.

BEYOND THE FIRST STEPS

In societies built for people without disabilities, walking has taken on an outsized importance. “Walking and standing is sexy,” says Jennifer French, co-founder of the Neurotech Network, a non-profit organization in St Petersburg, Florida, that is dedicated to helping people with impairments access neurotechnology devices. “It gets people excited.”

But walking isn’t everything, says Kim Anderson, a researcher at Case Western Reserve University in Cleveland, Ohio, and president of the North American Spinal Cord Injury Consortium. In 2004, she conducted a survey of nearly 700 people with spinal-cord injuries. Regaining arm and hand function was by far the highest priority for people with quadriplegia, followed by regaining sexual function. For people with paraplegia, the most desired improvement was in sexual function, followed by bowel and bladder control and reducing the risk of autonomic dysreflexia, a life-threatening condition characterized by a spike in blood pressure and a drop in heart rate.

After Stefanie Putnam broke her neck in a swimming pool, walking was the least of her concerns. The injury left her immobilized from the neck down, and she couldn’t breathe on her own. “I wasn’t thinking, ‘Let’s stand, let’s walk,’” she says. “I was like, ‘Let’s live.’”

Even after she regained the ability to breathe, she still had problems, particularly with maintaining normal blood pressure. Medication and three sets of corsets couldn’t keep it high enough to stop her from fainting. She would pass out six or seven times a day. She couldn’t drive a vehicle. She couldn’t be alone. And when she started taking university classes, her parents had to tape a sign to the back of

her wheelchair advising bystanders to tilt Putnam back if they found her unconscious. “I was so sick of doctors just telling me again and again, ‘This is the way it’s going to be,’” she says.

In 2017, Putnam moved to Louisville to join another of Harkema’s studies — focused not on walking, but on the cardiovascular system. For Putnam, the effects of stimulation were immediate and profound. She hasn’t passed out in months. She no longer needs round-the-clock care, and she can drive again. The other three participants in the study also showed significant improvements in their blood pressure⁹.

David Darrow, a sixth-year neurosurgery resident at the University of Minnesota Medical School in Minneapolis, has seen countless injuries like those sustained by Putnam and Summers. “It was kind of the worst part of my job,” he says. He would repair the structure of the spine knowing that there was nothing he could do to restore its function. So when he heard Edgerton talk about the promise of epidural stimulation at a conference in 2015, “I was just blown away,” he says. “I just couldn’t figure out why there weren’t like two dozen centres working on this.”

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Neurophysiologist Susan Harkema (standing, centre) with study participant Stefanie Putnam in 2017.

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Darrow suspected the findings might be bogus, but he wanted to find out for himself. So, he set out to design an entirely new kind of study. Other groups have tested epidural stimulation in combination with intensive rehab before and after the implant. Darrow wanted to know what effect stimulation would have on its own.

The study differs from the other trials in another important way: the experiments are not focused on standing or walking. His group is looking instead at voluntary movement and improvements in cardiovascular function, bladder and bowel function, and sexual function.

Darrow and his team have implanted ten people with stimulators, and in March they published results on the first two participants¹⁰. Both regained some voluntary movements, such as wiggling their toes and lifting their lower legs. They also saw improvements in bowel and bladder function. Stimulation also helped to regulate blood pressure in one person, and restored her ability to have an orgasm during sex. Darrow plans to implant ten more people, and to launch the next studies with the goal of getting the therapy to patients as quickly as possible. Epidural stimulation isn't a panacea, but that doesn't matter, he says. "I don't really believe in cure as part of my practice. I am all about making people's lives better incrementally."

FORWARD FOCUS

The demand for new therapies has given birth to a medical tourism industry for spinal-cord injuries. In Bangkok, the World Medical Center Hospital offers epidural stimulation — with or without stem cells — to anyone who meets its criteria and can afford the more than US\$70,000 price tag. As of July, the hospital, which is affiliated with a company called Unique Access Medical (UAM), had performed 70 implants, says Henning Kalwa, head of patient services. "While other colleagues in the field of neurology are still spinning their wheels with studies, trials, and FDA bureaucracy in the pursuit of a cure for paraplegia and quadriplegia, UAM is successfully treating patients," wrote Kalwa in a public post on LinkedIn.

Courtine cautions people with spinal-cord injuries against pursuing epidural stimulation outside clinical trials. He has seen stimulators implanted at the wrong spot, and he points out that even the leading scientists don't yet agree on how to configure the stimulation and do the training. "It's way too early," he says. Tansey fears that rushing to treatment could send epidural stimulation the way of stem cells — clinics could pop up offering unsupported therapies that might not work, and

serious research could fall by the wayside.

For the scientists, the focus is still on conducting research. Each group seems to have its own ideas about how to move the science forward.

Harkema's team continues to recruit participants for the Reeve-funded study. She has also begun a project looking at the effect of stimulation and training on bowel and bladder function.

Courtine, meanwhile, has co-founded a company called GTX medical in Eindhoven, the Netherlands, to develop a custom-made stimulator for people with spinal-cord injuries. He hopes the technology will be ready in a couple of years. His team is also launching a study to test epidural stimulation in 20 individuals who are less than a month into their recovery. In those people, "there's real potential to see a neurologic recovery", he says, and possibly even growth of new nerve fibres.

The Mayo team has just launched a study comparing transcutaneous stimulation with epidural stimulation. And Darrow is still recruiting participants for his study. "If it does work, even somewhat, we have a responsibility to scientifically and rigorously explore it and also deliver it in a timely fashion," he says.

Summers, meanwhile, is focused on putting one foot in front of the other. After the initial study ended, he left Kentucky and moved around the United States. Then, in 2018, he moved back to Louisville to participate in another study focused on standing, stepping and voluntary movement. He's now on his second stimulator, and the difference has been profound. The pulses are "crisper and cleaner", Summers says, and each day it feels like he hits a new milestone. On a Tuesday morning in April, he turns the stimulator on, straps into a harness suspended from a metal frame on casters, and begins taking halting steps down the long hallway on the twelfth floor of the Frazier Rehabilitation Institute in Louisville.

His girlfriend, Julie Grauert, wears a Team Reeve T-shirt and rolls along behind in Summers's wheelchair, blasting Disney tunes from her phone. "You got it, babe," she says. Their service-dog-in-training, a golden retriever named Bear, follows them.

Some steps look easy. Summers's grey Nikes swing confidently forward and land true. But the workout takes a toll. His legs shake, and occasionally his left foot lands at odd angles. For a moment, Summers's legs buckle and the harness catches him. "I'm just getting fatigued and frustrated," he says.

Summers's version of walking represents astonishing progress, and he continues to improve. But it is still an ongoing experiment. He can't yet take a walk in the park or even amble around his apartment.

A perpetual optimist, Summers views stimulation as nothing short of a cure. For him, the biggest benefits have been the least visible — improvements in blood pressure, bladder and bowel control, sexual function and temperature regulation. And there are the more trivial sensations, such as a deep appreciation for brand new socks. "I can feel the softness," he says. "It's crazy the little things that I find joy in." ■

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