STEP BY STEP

Could the scientist and the surgeon make a paralyzed man walk again?

BY SUSANNAH HICKLING

Dr. Pawel Tabakow and Darek Fidyka in the new neurosurgical unit at Wroclaw University Hospital.

As British neuroscientist Professor Geoff Raisman walked into the small sun-filled room at the Rehabilitation Centre for Spinal Injuries in Wroclaw, Poland, he instantly spotted the man in the wheelchair by the window.

Raisman couldn't help but feel anxious; he and Polish neurosurgeon Pawel Tabakow were about to embark on something that had never been done before. It might not work; it might even cause harm. But at the same time he was bubbling with anticipation. After decades of painstaking research, now in the spring of 2012 here was a chance to make a paralysed man walk again.

Darek Fidyka, the occupant of the wheelchair, shifted his gaze from the floor to look at the two doctors. Slim, handsome, in his thirties, he should have been in the prime of his life. He had loved dancing, hunting, playing football. But all that had been taken away from him two years before when his girlfriend's ex-husband had attacked him with a knife, severing his spinal cord and paralysing him from the waist down.

Tabakow explained to Darek that the pioneering procedure he was proposing involved two operations. In the first, surgeons would carefully remove one of his two olfactory bulbs located at the front of the brain just above the nasal cavities. These process messages from the nose and enable us to smell. They also contain special cells, olfactory ensheathing cells (OECs), which allow nerve fibres to renew themselves after damage from pollution or infection. Our sense of smell the only part of the nervous system that continually regenerates.

Darek's OECs would be cultured to produce many more cells before being injected into his severed spine in a second operation. The aim? To encourage the damaged nerve fibres in his spinal cord to regrow.

Both interventions were delicate and offered no guarantee Darek would regain even a flicker of movement in his legs. The builder and volunteer fireman from a small village about 160km from Wroclaw listened intently and fixed his piercing grey eyes on Raisman, the pioneering scientist who had first discovered how cells from the olfactory system regenerated.

"Ask him why he wants this operation to be done," Darek said to Tabakow.

Raisman paused, feeling the weight of responsibility. In Europe alone 333,000 live with spinal cord injury.

"Well, the science tells us that's what we should do," Raisman replied, placing his hand on Darek's shoulder.

PREVIOUS SPREAD PHOTO BY PIOTR MALECKI/GETTY ASSIGNMENT

"OK," said the patient after a brief pause. "Go ahead." Raisman had won Darek's trust.

For Geoff Raisman, now 76, the work that had led to this moment had started in the late 1950s while studying medicine at Oxford University. He had access to a revolutionary new device, the electron microscope, which offered magnifications never before possible. Raisman began researching the brain. Over the next two decades he would make two stunning discoveries.

The first was plasticity. It had long been believed that each brain cell had a fixed number of connections, provided by nerve fibres that connect different groups of cells, and that, once destroyed, no new connections were possible. However, using the electron microscope, Raisman saw that where nerve fibres had been irreparably damaged, fibres of neighbouring cells would make a precise replacement of the lost connections.

It took ten years for plasticity to be accepted, but Raisman forged ahead with his research. He found that even cut nerve fibres could send out new shoots. However, they failed to effect a successful repair, because cells that arrived to provide a pathway for the new nerve fibres also created scar tissue that prevented fibres from reaching their destination. Raisman called this second discovery the Pathway Hypothesis.

He began to think about how nerve fibres might penetrate this barrier of scar tissue—if they could, paralysed people might walk again. Nerve fibres were like cars on a highway that come upon a bridge that has been washed away. They find other routes, still getting from A to B but not as quickly or effectively. Could OECs provide a bridge in the spinal cord and repair the highway, restoring function?

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In 1985, Raisman took to the electron microscope again to find out more about OECs. What he saw was groundbreaking—OECs provided a conduit for olfactory nerve fibres as they regrew and, as the fibres approached the brain, the OECs threw out tiny feelers. The pathway cells in the scar tissue responded, reaching out with arms of their own and ushering in the new fibres.

Convinced he was onto something, the neuroscientist and his team painstakingly perfected an ultra-precise technique to transplant OECs into the spinal cord, using laboratory rats. Initially, nothing happened. Then one

Darek speaking with Professor Raisman, left, and Dr. Tabakow, middle, in the Rehabilitation Centre for Spinal Injuries after his operation.

night in December 1996, Geoff Raisman was unable to sleep. Sitting in front of the rats' cage at 2 a.m. in his lab in London, he offered the smallest rodent a tiny piece of dried noodle. Suddenly, the tame creature tentatively held out her disabled paw. She did it again. *Yes,* Raisman realised, *we can repair the nervous system.* Within days, all the rats were using their previously disabled paw.

Pawel Tabakow had been fascinated by Geoff Raisman's research since he was a student and now wanted to collaborate with him. "In his papers, he went deep into the detail of cell interaction," says Tabakow. "He was very strict in what he was saying, writing, thinking."

In 2005, Tabakow and his team flew to a conference in Hong Kong where the British neuroscientist was speaking. The young Polish surgeon waited to talk to Raisman, finally catching a minute with his hero. But Raisman was dismissive. He knew of too many neurologists who had started transplanting cells into desperate patients with spinal injuries—often for large fees—while ignoring the unanswered questions in his work.

Tabakow persisted. Raisman finally went to see him in Wroclaw, where he was building a new neurosurgical unit at the Wroclaw University Hospital, and was impressed at the neurosurgeon's determination and logical approach.

Although his work was funded by the U.K. Stem Cell Foundation, Raisman needed more funding to keep going with his research, now based at University College London's Institute of Neurology. Benefactors—especially of the corporate variety—wanted faster results than he could produce.

PHOTO: © GETTY IMAGES

One day in 2006 he received a call from David Nicholls, group director of food and beverage for Mandarin Oriental hotels. His son Daniel had been paralysed in a swimming accident in 2003 in Australia at age 18. Nicholls' research showed there had been little progress in finding a cure for paralysis, but Geoff Raisman's name kept coming up. At the same time, Nicholls set up the Nicholls Spinal Injury Foundation (NSIF). He was now looking to invest in spinal injury research.

Nicholls wanted to meet Raisman. "He was a bit of a maverick," he says. "I enjoyed that. He was also the only scientist I had ever spoken to who said that paralysis was curable."

Nicholls' foundation has so far given Raisman and Tabakow more than £1 million. So convinced is Nicholls of the importance of their work that NSIF funds no other project, even though there are no guarantees the treatment will ever benefit his son. "Even if it couldn't help Daniel," Nicholls reassured Raisman at one meeting, "we'd just be delighted that no other family would have to go through what we've gone through."

It is in large part thanks to Nicholls' investment that Darek Fidyka's revolutionary treatment was possible. Tabakow had first met Darek in his clinic at the end of a long day, but when he learnt that this patient had a chronic sinus condition which required surgery, his tiredness evaporated. The surgery Darek needed would expose the olfactory bulb, making him the ideal patient for the first OEC transplant. What's more, Darek seemed to have the inner strength to cope with the burden of expectation and the eight months of intensive physiotherapy he would need before surgery to rule out any likelihood that he could get better on his own. There would also be physically demanding rehabilitation after the treatment.

For Darek the decision to go ahead was never in doubt. "It was the only therapy the doctors offered that might give me a chance to walk," he says. "It doesn't matter if I'm the first to have it. I told myself things couldn't be worse than they were."

Two weeks after the first operation to repair Darek's sinus and remove his olfactory bulb, Raisman watched as Tabakow and his team transplanted the cultured OECs into Darek's spine.

The atmosphere in the operating theatre was tense. There were fewer cells than hoped, leaving no margin for error. But before they could be transplanted in 100 micro-injections, surgeons had to expose Darek's spinal cord, layer by delicate layer, revealing a huge 7mm gap.

Tabakow and his colleagues injected some of the cultured cells into

Today, Darek spends much of his time in physiotherapy at the rehab centre.

PHOTO: © GETTY IMAGES

a thin strip of scar tissue on the right of the spinal cord, but most were inserted above and below the gaping wound. To bridge it, Tabakow took four small strips of nerve fibre from Darek's ankle and laid them across the gap on the left-hand side of his spinal cord, hoping this would encourage the regenerating cells to enter the spinal cord tissue.

It was a slim hope. Despite gruelling physiotherapy five hours a day five days a week after the operation, Darek showed no improvement. These were dark days for the patient. "I knew how much pain and determination I had invested in this," says Darek, now 41. "I was afraid maybe it was all for nothing." But he kept going, spurred on by his family—his mother has been constantly at his side at the rehab centre in Wroclaw—and an intense desire to regain his independence. Then, after four months, came the first signs: more muscle in his left leg, pins and needles, sensations of hot and cold. The exercises were easier too. He managed to turn the exercise bike, an impossible feat before surgery.

"What am I looking at?" David Nicholls was on the phone to Geoff Raisman, who had sent him a series of MRI scans. "I'm looking at a patient with a spinal cord injury and then I'm looking at a complete spinal cord."

"It's Darek's," Raisman replied.

"It can't be, it's repaired."

"David, it's his."

Nicholls fell silent. The promise these grainy pictures held for so many condemned to life in a wheelchair filled him with excitement.

Raisman was equally exhilarated, and never more so than when he returned to Wroclaw in December 2013. He watched as Darek moved forward with the help of leg braces and parallel bars. His gait was laboured and twisted, but he was walking. Darek's left leg was clearly gaining muscle and strength—a development consistent with Tabakow's cell-bridge repair on the left-hand side of his spinal cord—and, while his right leg was weaker, he had recovered sensation in it down to his foot. Nerve fibres of sensation, even from the right side of the body, cross over and travel up the left-hand side of the spinal cord to the brain.

That was the proof Raisman needed. *We've done it!* he thought. Tabakow now plans to carry out the operation on more patients with a similar injury to prove the technique really works. Nicholls is committed to helping to fund this expensive next stage. He aims to raise £10 million for development work in Poland and the U.K. His foundation has already bought vital equipment for the rehabilitation centre in Wroclaw.

Whether or not his efforts ever benefit his own son, he wants to contribute to the development of a cure. "You don't want to see the ripple effect that paralysis causes—the pain, the despair," he explains. "If we can stop people going to that place, what we've done will be worth it."

Darek can now get around with a walker and drives a specially adapted car. His sex life has improved, and he can also feel his bladder and bowel. "I have started to feel human in the fullest sense," he says. He is hoping one day to be able to help other people with spinal injuries become self-reliant. But currently he is focussed on his therapy and spends most of his time in the rehab centre.

For now, it's the tiny things most of us take for granted that give him most joy. "When the muscles contract it's an indescribable feeling, like a new birth," Darek says. ■

ON THE HORIZON

OTHER DEVELOPMENTS that might one day help the paralysed walk:

■ **NEURAL STEM CELLS** These cells can make any of the three major kinds of cells found in the central nervous system and would be transplanted into an injured spinal cord. Trials are under way in the United States, with plans to expand to Canada.

■ **"BIONIC" IMPLANT** Scientists from the École Polytechnique Fédérale in Lausanne have developed a flexible electronic implant that delivers electrical and chemical signals when inserted into the spinal cord. It successfully enabled spine-injured rats to walk, but human use is still many years away.

■ **NEW DRUG** A compound, intracellular sigma peptide, discovered by U.S. scientists, has yielded promising results on rats. Injections of the drug aim to break down the barrier of scar tissue preventing new nerve connections in the spine. Human trials are still a long way off.