In search of a miracle

Paralysed patients are looking to scientists working on spinal-cord regeneration to help them walk again. Is this pressure causing too much faith to be placed in preliminary, inconclusive results? Helen Pearson investigates.

Inspiration: patients with spinal injuries have been given hope by the impetus for research provided by the paralysed actor Christopher Reeve (inset).

SPL; T. WIMBORNE/REUTERS (INSET)

It was a miracle of almost biblical proportions. In 1998, scientists in Israel revealed that rats whose spinal cords had been severed had walked again after an injection of healing immune cells called macrophages[1]. Their hopes buoyed by enthusiastic media coverage, paralysed patients began to dream of taking their own tentative steps.

Five years on, the status of those dreams remains unclear. Proneuron Biotechnologies, a Los Angeles-based company founded on the back of the research of lead investigator Michal Schwartz at the Weizmann Institute of Science in Rehovot, is expected soon to release the results of an initial trial of the procedure on eight patients with spinal injuries. Media reports have indicated that some patients have recovered some feeling and movement, but many researchers do not expect a repeat of the rodent miracle. Indeed, they claim that at least one group has since tried, and failed, to reproduce Schwartz's original animal results.

Schwartz's study is not alone in this regard. Over the past few years, scientists working on spinal-cord repair have revealed encouraging results on several occasions, only to find that other groups have struggled to recreate the same outcome. Three papers published in *Neuron*[2–4] last month underline the point, reporting contradictory findings in parallel studies of 'knockout' mice lacking proteins that are believed to be among the main inhibitors of nerve growth in the spinal cord. "Reproducibility has been a major problem in spinal-cord injury," says Oswald Steward, director of the Reeve-Irvine Research Center at the University of California, Irvine.

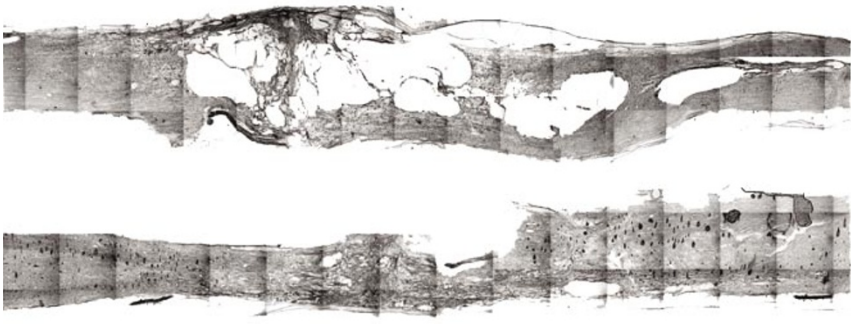
Some think that the problems are simply technical: repairing a rat's string-thin spinal cord is a complicated experiment to copy. Others argue that, in some cases, eager scientists have put an over-optimistic spin on their results. These accusations are hotly disputed, but some researchers privately fear that the expectation of high-profile patient-advocacy groups may be inadvertently creating an atmosphere in which problems are likely to occur. Certainly, some researchers admit to feeling under pressure to perform. "If patients phone you three or four times a year and you can't tell them anything new, that's a pressure," says Isabel Klusman of the University of Zurich in Switzerland.

Delicate balance

Exploring these issues is difficult, as no one wants to be perceived as criticizing patient groups. In particular, researchers say that they owe an immense debt of gratitude to the Hollywood star Christopher Reeve, who was paralysed in a horse-riding accident in 1995. His public determination to recover — and his inspirational support of the science that might help him to — has drawn millions of dollars into research, both directly through the Christopher Reeve Paralysis Foundation and indirectly through government budgets.

This impetus intensified interest in a finding reported in 1980, which provided the first glimmer of hope that a damaged spinal cord might be repaired. Albert Aguayo, now at McGill University in Montreal, Canada, cut rats' spinal cords and showed that they were able to sprout into pieces of tissue grafted from the animals' sciatic nerves[5]. This seeded the idea that the lack of regrowth following a spinal injury is partly caused by inhibitory molecules in the spinal cord itself.

Although Reeve's advocacy has undoubtedly brought more funding for research, it has also meant that promising scientific discoveries have been more likely to become



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Road to recovery? A damaged rat spinal cord treated with immune cells (bottom) looks to be in better condition almost half a year after injury than cord that was not treated with the cells (top).

front-page news. One study from 1996, for example, received massive coverage. Henrich Cheng at the Karolinska Institute in Stockholm, Sweden, showed that paralysed rats were able to move their legs again after he coaxed spinal nerves to grow across their severed spinal cords. To achieve this, he built 18 tiny bridges of nerves taken from between the ribs and added a growth-promoting protein[6].

For more than six years, no one published a duplication of the results. Eventually, researchers led by Vernon Lin at the Long Beach Veterans Affairs Medical Center in California managed to reproduce Cheng's main findings[7]. Lin regards human trials as premature, but Cheng has moved ahead, operating on 40 spinal-injured patients in Taiwan. He expects to publish his results later this year.

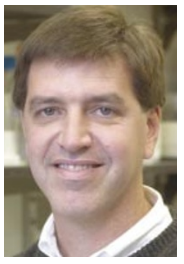
Technical trauma

Neuroscientists agree that, in large part, the problems with reproducing studies lie in the technical difficulties. "We're trying to do one of the most difficult things in science," says spinal-cord researcher Wise Young of Rutgers University in Piscataway, New Jersey. Cheng says that he took a year to learn how to build the delicate bridges across a severed spinal cord. "We gave up after six months," says Young.

Another problem is that scientists do not always compare like with like. Each group tends to use its own model of injury — including those that crush the spinal cord, or sever it partially or completely. Crushing more closely mimics a typical human injury, but cannot be compared with severing the cord.

Researchers have also struggled to accurately measure and compare improvements in animals' movement after treatment. In another widely debated study, Almudena Ramón-Cueto, now at the Spanish national research council's Institute of Biomedicine in Valencia, reported that cells taken from an adult rat's olfactory bulb, the first staging post in the neural perception of smell, and transplanted into a severed spinal cord, helped paraplegic animals to walk again[8]. Most experts agree that these 'olfactory ensheathing cells', which normally help nerve cells grow projections from the nose to the brain, can help nerves to grow across a site of injury. But subsequent studies have been difficult to compare with those by Ramón-Cueto, partly because the team assessed the animals' recovery by judging their performance in climbing on a wire ramp — a test not used in other labs.

Although technical difficulties may be part of the problem, some experts argue that the field is also plagued by premature enthusiasm. If, after treatment, only one or two nerves grow across a severed cord, this could be seen as a disappointing result. Yet, given the normally barren appearance of such a wound, some researchers might describe the same result as a stunning success. "They're seeing what they want to see," claims Fred Gage, a neuroscientist at the Salk Institute for Biological Studies in La Jolla, California.



M. YOUNG

Marc Tessier-Lavigne (top) and Stephen Strittmatter tried to reconcile conflicting results.

Researchers whose results have proved difficult to repeat reject any suggestion that they may have been guilty of excessive enthusiasm. "There was no over-interpretation," says Schwartz, "I'm standing behind every word I said." Nir Nimrodi, chief executive of Proneuron, says that the company has replicated and expanded on Schwartz's animal studies, but has not yet published the results, for reasons of intellectual property. Cheng, meanwhile, says that the data from his experiments and the surgical experience of his team gave him the confidence to transfer the technique from the rat model to patients.

Susan Howley, director of research at the Christopher Reeve Paralysis Foundation, based in Springfield, New Jersey, argues that good scientists should not be unduly influenced by patients' desire for good news. Ultimately, she stresses, patients are the losers if preliminary results over overplayed. "They are on a yo-yo," Howley says — buoyed up by one positive result, only to be crushed by the failure of subsequent studies to repeat it.

How can this roller-coaster experience be avoided? One positive sign is an initiative established last year by the US National Institute of Neurological Disorders and Stroke in Bethesda, Maryland. The $8-million, five-year Facilities of Research Excellence in Spinal Cord Injury programme will devote a proportion of its budget to determining which animal studies are worth pursuing into the clinic. Independent investigators will be encouraged to work with the labs that first report promising findings to ensure that techniques are comparable. "We need to know what is working and under what conditions," says programme director Arlene Chiu. The initiative will also help to develop more quantitative and objective scales to measure animal recovery.

Other experts take solace from the authors of the three papers published last month in *Neuron*, all of which focused on proteins made by a gene called *nogo*. One of the proteins, called Nogo-A, is present in the myelin sheaths that wrap up nerves in the spinal cord, and is thought to help prevent nerves from growing back into an injured site. The three groups, led by Stephen Strittmatter of Yale University in New Haven, Connecticut, Martin Schwab of the University of Zurich and Marc Tessier-Lavigne at Stanford University in California, genetically engineered mice to lack Nogo-A. Strittmatter's group found massive regeneration and improved gait after a spinal-cord cut[2], Schwab found some regeneration[3], and Tessier-Lavigne found none[4]. The reason for the varied results is unclear, but one possibility is that minor differences in the way that the genes were inactivated affected other proteins that block or boost nerve growth.

Rather than racing each other to publish their results separately, allowing patients' hopes to be raised and then dashed, the researchers agreed to work in consultation. Tessier-Lavigne and Strittmatter realized they were doing similar experiments when they met at a 2001 conference, and later approached Schwab. Tessier-Lavigne even sent some animals and a postdoctoral researcher to Strittmatter's lab to try to ensure that they were making the same type of injury.

Mary Bunge, of the Miami Project to Cure Paralysis at the University of Miami School of Medicine in Florida, argues that similar collaborative approaches must be more widely adopted in order to solve the problems of reproducibility plaguing the field. "It's very important that we all get together and talk about it," she says. ■

Helen Pearson works in *Nature*'s news syndication team.

1. Rapalino, O. *et al. Nature Med.* **4,** 814–821 (1998).
2. Kim, J.-E. *et al. Neuron* **38,** 187–199 (2003).
3. Simonen, M. *et al. Neuron* **38,** 201–211 (2003).
4. Zheng, B. *et al. Neuron* **38,** 213–224 (2003).
5. Richardson, P. M. *et al. Nature* **284,** 264–265 (1980).
6. Cheng, H., Cao, Y. & Olson, L. *Science* **273,** 510–513 (1996).
7. Lee, Y. S. *et al. Neurotrauma* **19,** 1203–1216 (2002).
8. Ramón-Cueto, A. *et al. Neuron* **25,** 425–435 (2000).