ONE SMALL STEP FOR A MAN...

Last year, an experimental treatment helped a paralysed man to walk again, sparking headlines across the world. **Professor Geoffrey Raisman**, who led the UK research team, explains how it all began.

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After many furious jabs, the blade finally found its mark and slipped deep between two vertebrae. It was 2010 when Darek Fidyka collapsed from multiple stab wounds in a forest at night, far from help.

From that moment on, he was paralysed from the waist down and without sensation. In the hours to come, he could no longer control his bowels or bladder, and would lose his sexual function. His spinal cord had been completely severed. No one had ever recovered from this injury before.

I had been working for years on rat models of spinal cord injury and believed I had a cure. Dr Pawel Tabakow, a young neurosurgeon in Poland (the victim was Polish), had been shadowing my work for many years. A consultant neurosurgeon in the department of neurosurgery at Wroclaw University Hospital, he was determined to try out my methods and work out how to scale up from our microscopic rat injuries to the amount of damage suffered by his patient.

He evolved a new operation, which I will call the cell/bridge technique. After this operation, the patient slowly started to walk again with assistance, to feel again and to regain some sexual function.

For me, the story began in the cold winter of 1947. The whole hillside in Meanwood, Yorkshire, had been covered with a thick, sloping blanket of snow that was, like a glacier, weeping great runnels of meltwater, joining, separating and again re-joining, flowing into the ice-cold waters of the stream below. I wondered how the sticklebacks and minnows in that stream would survive. How could such tiny living

Darek Fidyka learns to walk again after pioneering surgery

things resist the great extremes of nature? In a word, I became a naturalist. What else is a naturalist but someone who looks at the natural world, questions, wonders and admires?

When I was a third year medical student my mentor, Max Cowan, persuaded me to do a PhD project on the connections of the hippocampus. Through the microscope, I was able to get a peek into one tiny nexus in the vast tracery of connections that make up the most amazing and most elaborate structure that evolution has produced – the brain.

There was one great puzzle that eluded us. During development, nerve cells grow long fibres to reach their destinations. When severed by adult injuries, they do not grow. However, the end of the fibre, which remains connected to the cell body, sprouts vigorously as if seeking to regain its former target. The sprouts, though, remain blocked at the site of injury – they are unable to re-establish their former contacts. This is the pattern of spinal cord injury.

Scientific advances and technology go hand in hand, and at about this time procedures became available to allow the powers of the electron microscope to examine the structure of the brain. Sanford Palay, in 1955, had been the first to see synapses, the elaborate, jewel-like arrangements at the point where one nerve cell makes contact with another.

Now, with this tool, I found that synaptic configurations seemed to change after injury. What caught my eye was a puzzling structure where a single fibre terminal made more than one connection. I was able to show experimentally that these double synapses resulted from an intact fibre taking over the territory vacated by loss of a connection.

In 1969, I called this plasticity, and wondered if this could be the basis of memory.

The key point was that the adult brain was forming new connections after injury. I was to find that this was an unacceptable idea at the time: society was too rigid to imagine the adult brain was anything but perfect.

However, things were changing, hierarchies were breaking down, and in time plasticity became accepted. In fact, I am beginning to think that plasticity is the core function of the brain; the ability to change, always to adapt to the changing situations of life, to learn, to remember, and to forget – that deep core that makes the brain the key organ in the evolutionary struggle for survival.

> **“The pattern of the OECs suggest they exert a unique door-opening effect at the surface of the brain”**

However, there were much more practical questions at hand. If cut nerve fibres sprout, and if intact nerve fibres can establish new synaptic connections, why were spinal cord injuries irreparable?

My speculation was that adult nerve fibres can regenerate after injury and can re-establish their original connections. They were not at fault, but what was lacking was a pathway to lead them back to their original destinations. Later, I called it the Pathway Hypothesis. It is still a hypothesis. But what is the use of a hypothesis if it can't be tested? The only proof of the hypothesis would be if it were possible to reconstruct the pathway and show that nerve fibres could grow back, re-establish their former connections and restore lost functions.

I puzzled for years about how a pathway could be re-established. The molecular mechanisms that would be needed to bring about the cellular interactions of such a complex reorganisational event were well beyond current knowledge. How could we hope to achieve it?

The solution came from observations on the olfactory system. From the 1960s onwards it was becoming known that the olfactory nerves have the unique property of continual replacement throughout adult life. As a result, the fibres are continually entering the brain and forming new connections. Something in the olfactory system must be providing a permissive pathway for these events.

In 1985, I showed that at the point where the olfactory nerves enter the brain, there is a special type of glial cell. These cells are called olfactory ensheathing cells (OECs). Seen through the electron microscope, the arrangements of the OECs suggest they exert a unique door-opening effect at the surface of the brain.

Together with two Chinese colleagues, Ying Li and Daqing Li, with whom I have been working for nearly 30 years, we showed in 1997 that transplantation of OECs cultured from the adult rat olfactory bulb can provide bridges for severed nerve fibres to cross a minute injury of the rat corticospinal tract, re-establish connections and restore lost functions.

Dr Pawel Tabakow, one of the neurosurgeons who was enthused by this finding, spent some years learning the properties of human OECs, developing the surgical approach and the equipment to enable him to inject them into human spinal cord injuries, and demonstrating the safety of the operation.

There was one final problem in scaling up from the rat to the human situation. In dealing with the minute rat injuries, we could easily obtain enough cultured OECs to form a physical bridge across the injury. The number of OECs that could be obtained from biopsy samples of a patient's olfactory system might just cover a pinhead, but most human spinal cord injuries are the size of a thumb.

Tabakow chose the patient with the knife injury as having the cleanest severance of the spinal cord with the least gap between the stumps. Nonetheless, the separation of the stumps was almost a centimetre – a separation far beyond what could be bridged by the number of cells available. To deal with this, Tabakow introduced another element.

It had been shown that the introduction of strips of limb nerve into the spinal cord can induce growth of damaged spinal nerve fibres. So, after injecting the OECs into the stumps, Tabakow took four tiny strips of nerve from the patient's ankle and laid them as bridges across the gap.

Darek Fidyka with Dr Pawel Tabakow (speaking), the neurosurgeon who changed his life

Within a month, Fidyka started to recover muscle mass in the leg and sensation. After intensive rehabilitative physiotherapy, he is now able to walk with a frame and can resume much of his former life. His family life is restored: he can drive a car, is independent, and can go out hunting with his friends in the forest. “It was,” he said, “like being born again.”

Only repeating this operation will tell us if this ‘miracle’ can work again.

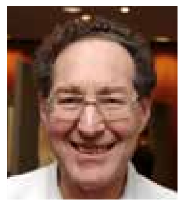
Yet there is about these events a frisson, a tingling. What if the time has come for spinal injury to be cured? And after that, what about all the other injuries where nerve fibres are disconnected – such as stroke, blindness, deafness? Do we stand on the threshold of history? If we do, there is an immense mountain to be climbed.

For me, this story began with that sense of wonder at the sticklebacks and minnows in Meanwood Beck. The first of nature's gifts to me was the observation of double synapses. From there, half a century of winding paths led through the olfactory system to a patient getting out of a wheelchair.

I could not have anticipated the outcome. What led me on was the sense of wonder at nature, and whoever studies nature enters a magical world, a world of enchantment and delight. To anyone thinking of starting on their journey of discovery, remember Longfellow:

“A boy's will is the wind's will,
And the thoughts of youth are long, long thoughts.”

BIOGRAPHY



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