

# Paper chase

Thousands of patients are queueing to be treated by Hongyun Huang at his Beijing clinic. But no Western journal editor seems willing to publish his research. **David Cyranoski** talks to the neurosurgeon whose global reputation among the ailing hasn't swayed his peers.

**R**enowned German artist Jörg Immendorff is used to causing a stir. But when he flew to China this March to receive an unconventional treatment for his neurological disease, he provoked uproar at home. His doctor scolded him for trying a therapy that was unproven. And newspapers warned of the possible rise of medical tourism to China based on false hopes.

Immendorff was undeterred. He suffers from ALS, or amyotrophic lateral sclerosis, a progressive disease that is slowly breaking down his nerve cells and destroying his muscle control. The condition is incurable, and Immendorff was willing to try nearly anything to alleviate his symptoms. "I see myself as part of an experiment," he told the German newspapers.

The artist's destination was the clinic of Hongyun Huang, a neurosurgeon at Chaoyang Hospital in Beijing. It was Huang who developed the treatment — and it was Huang who injected two million cells from an aborted fetus into Immendorff's brain.

Since 2001, Huang has used cells taken from nasal tissue in fetuses to treat some 600 patients with a number of neurological problems, from spinal injuries to degenerative disorders such as multiple sclerosis and Parkinson's disease. He claims a high success rate, but says he uses the treatment only as a last resort. "Many diseases have no cure," he says, "and we need to try new methods."

Many of Huang's patients are effusive in their praise for the unconventional therapy. But it remains anathema outside China — his critics argue that his results are supported by little more than anecdotal evidence.

This divide presents something of a dilemma. Medical scientists want to see new treatments put through rigorously controlled studies and are suspicious of claims not backed by scientific evidence. A strong patient following is not enough to demonstrate the efficacy of a novel approach, particularly given that desperate patients are eager to try anything that may help. On the other hand, a physician who believes a treatment is working might resist performing placebo controls as these seem unethical. This can leave patients caught in

the middle — unsure of the science, they will often seek the treatment whether or not the research has been done.

Among his patients, Huang has treated about 400 with spinal cord injuries and 100 with ALS. Some who have received the therapy claim that they have improved hand motion and feeling in their fingers. Others report better bowel control and greater ease of breathing. Huang admits that not all of the patients who receive the US\$20,000 treatment respond, but he claims that most do. And he says there is no evidence of serious side effects. As a result, his reputation among patients has spread. Some 3,000 Chinese and 1,000 foreigners are now lined up for the fetal-cell injections.

## On a mission

Distracted in an office bustling with assistants, Huang says he is confused over why the Western academic world won't recognize him. He has published nine papers in Chinese journals, including one written in English<sup>1</sup>. But despite his claims of clinical success, Huang says that his latest manuscript has been rejected by several of the top international journals, including *Nature Medicine*, *Science*, *The Lancet*, *The New England Journal of Medicine* and the *BMJ*. Huang says his results should be seen as a revolution in clinical treatment, and that rejection is pure discrimination — a refusal to take a serious look at a new method developed by a researcher in China. "If this came from Eng-



**Hongyun Huang (left)** claims that his technique of injecting fetal cells into patients can improve the quality of life for people with spinal injuries.



land or the United States, it would have already been published," he says.

Many observers disagree with that assessment. They say that the real problem with Huang's work, which he has presented at several international meetings, is the difficulty of measuring his results. For the most part, they are anecdotal. Huang uses videotapes of individual patients and relies on their own assessment of their progress. Such self-assessment is not always consistent. German newspapers reported that Immendorff, for example, felt he could move his hands better after the surgery. But later he said that the treatment hadn't really had any effect.

Unlike proposals to use stem cells to treat conditions such as ALS, Huang's cell injections are not intended to replace damaged nerve tissue. Instead he uses olfactory ensheathing cells (OECs) to promote healing through the production of proteins called growth factors that stimulate cells to grow and divide. OECs are believed to be responsible for the olfactory system's unique and still mysterious ability to sprout new connections to the central nervous system throughout a person's lifetime<sup>2</sup>.

Studies in animals suggest that OEC transplants can help to repair damaged nerves. This was most dramatically illustrated in 2000, when Almudena Ramón-Cueto, a neuroscientist at the Autonomous University of Madrid, used the cells to give paralysed rats the ability to use their legs<sup>3</sup>. Geoffrey Raisman, a neurobiologist at London's National Institute for Medical Research, has seen similar results. Raisman has been working with OECs since the 1980s, and has found that the cells can significantly improve breathing difficulties in rats with spinal injuries<sup>4,5</sup> — in humans, breathing problems can chain patients with spinal damage to a ventilator.

### All on tape

In his office, Huang plays videos of patients taken before and after the OEC transplant. Before, one ALS patient moves forward in a jerky motion and needs a crutch. His speech is limited to unintelligible mumbling. A month after surgery, the same patient gives a clearly enunciated introduction and, after a struggle to stand, moves forward without a crutch and more smoothly than before. Another who couldn't hold a cup for ten years is shown, post-surgery, signing his name with a pen.

More quantitatively, Huang scores some patients on tests designed by the American Spinal Injury Association (ASIA) and the International Medical Society of Paraplegia. Using the ASIA test, which measures the patient's ability to move, and to feel a light touch and pin pricks, Huang has reported some improvement after the transplant in patients with spinal-cord injury<sup>1</sup>.

Since Huang began performing the operations, enthusiastic reports from patients have been broadcast in news reports and Internet discussion groups. Among his champions is Donald Debolt from east central Illinois, who was paralysed in an accident in 1994. He says that he is still improving following his surgery in May 2004. "I was recently able to fasten a button for the first time in 11 years," Debolt says. Increased muscle development in his arms, back and abdomen are a great help when his wife struggles to get him in and out of his wheelchair, he adds.

Laura Jackson, who was paralysed below the neck in a cheerleading accident in May 2003, couldn't breathe on her own for more than five minutes before the surgery. Now she can stay off the ventilator for two hours at a time, and she has regained some trunk movement and sensation in her fingertips. "Was all of it from the therapy? No. Was most of it? Yes," says Daryl, Laura's father.

But not all patients are satisfied. Francis Catena, a major in the Belgian army until a fall broke his spine, says that despite modest improvements in movement and sensation, his therapy was not worth the hassle or the money. Reached at his home in Thailand, Catena complained of unsanitary hospital conditions in Beijing. He adds that his own doctor raised



Chaoyang Hospital in Beijing, where Hongyun Huang carries out his fetal-cell transplants.

questions about whether the surgery had been done properly. "I've seen amazing recoveries from Huang's procedure with my own eyes," Catena says, "but I expected more."

Patient testimonials and video tapes hold little sway with Huang's research peers. According to Raisman, the fundamental problem with Huang's studies is the lack of proper controls or any independent analysis of the data. "He needs to carry out studies for a significant length of time before and after the surgery with a degree of independent assessment," Raisman says. "His studies are not advancing things."

### Hard to measure

Martin Schwab, a neuroscientist at the University of Zurich, agrees that lack of careful quantification of the patients leaves evaluation of the procedure reliant on reflex testing and other subjective factors that might produce a placebo effect. "Videotapes and anecdotal evidence are clearly not acceptable as scientific evidence," he says. More compelling evidence

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— Daryl Jackson

might be possible if Huang used magnetic resonance imaging or electrical recordings of muscle activity to demonstrate changes in neural circuitry, suggests *Nature Medicine's* editor Juan Carlos López. "These would be quite convincing data," he says.

Without such studies, it is difficult to know whether the surgery is worth the risks. Although a number of animal studies using OEC to treat spinal-cord injury have been published, work in animal models of ALS or other neurodegenerative diseases has yet to reach this stage. Such work is normally a prerequisite for gauging the safety and efficacy of a treatment in humans. Furthermore, as the

fate of the cells once they are injected is not well understood, there is cause to worry about side effects, Schwab notes. "They could trigger inflammatory processes which, within the intact central nervous system tissue, would have catastrophic consequences," he says.

Huang counters that he has received approval from his hospital's ethical review board, and he insists that the safety of the procedure has been proven. Although he concedes that there is room for improvement — so far he has not used tissue-type matching to reduce the chance of the cells being rejected, for instance — he argues that it is time for action, not more animal studies. Scientific or not, that argument has a strong appeal to patients. "There are more animal and mouse studies than the world can take. We're ready for the real thing," says Daryl Jackson.

Huang's detractors say that tissue matching, as well as controlled studies, should have been a top priority from the very beginning. They add that this gap between Huang's approach and that of the mainstream biomedical research community will only make it more difficult for him to win general acceptance for his therapy — and to get published.

In the face of the repeated rejections, Huang says he is going to give up trying to convince a Western scientific community that, he is convinced, is prejudiced against him. "It's their loss. If they believed my results, it could dramatically change clinical practice," he says. And the patients are lining up whether or not his work is published.

**David Cyranoski is Nature's Asian-Pacific correspondent. Additional reporting by Sonja Schubert and Quirin Schiermeier in Munich.**

- Huang, H. et al. *Chin. Med. J.* **116**, 1488–1491 (2003).
- Ramón-Cueto, A. & Valverde, F. *Glia* **14**, 163–173 (1995).
- Ramón-Cueto, A., Cordero, M. I., Santos-Benito, F. F. & Avila, J. *Neuron* **25**, 425–435 (2000).
- Li, Y., Field, P. M. & Raisman, G. *Science* **277**, 2000–2002 (1997).
- Li, Y., Decherchi, P. & Raisman, G. *J. Neurosci.* **23**, 727–731 (2003).