# Fetal Transplants Show Promise

In early clinical trials, brain implants of fetal tissue have improved the conditions of patients with Parkinson's disease, leading researchers to call for expanded studies

When the U.S. government banned the federal funding of transplantation research using fetal tissue from induced abortions in 1988, the issue was more of theoretical than practical interest. While researchers hoped fetal tissue transplants might ultimately be used to reverse the symptoms of degenerative brain diseases such as Parkinson's and Huntington's, they had little evidence to support that idea. But 4 years later the encouraging clinical results have begun piling up—as was made clear by a parade of basic scientists and clinical researchers at the Fourth International Symposium on Neural Transplantation.*

And that's made the problem of the government's position on fetal tissue research much more immediate. With the ban on federal funding still in place and the feasibility of the government's plan to set up a fetal tissue bank using material only from spontaneous abortions in doubt (see next page), U.S. scientists say their research is being held back. According to John R. Sladek Jr., director of the Neuroscience Institute at the Chicago Medical School, "the ban is the biggest impediment to clinical progress that we can imagine." Sladek and others are frustrated because they think the time is ripe to undertake larger clinical trials—a move already planned in Europe. "We would like NIH to fund a small number of centers to carefully and systematically test the surgery," said neurosurgeon Roy Bakay from the Emory Clinic in Atlanta, Georgia. "If not, it will be done in a haphazard way, and it will take years."

Why do researchers such as Sladek and Bakay think that the time has come for expanded clinical trials? The answers came thick and fast at the recent conference. Clinical trials, conducted either abroad or with private funding here, are already showing that fetal tissue implants can significantly improve the symptoms of Parkinson's disease. Indeed, the Europeans are sufficiently encouraged by these early studies that they are organizing a large trial, to be conducted at up to 15 research centers in 11 countries. Additional work on animal models reported during the meeting strongly suggests that appropriate fetal tissue implants might also help patients with Huntington's disease, a fatal, inherited brain degeneration that strikes in mid-life.

But just in case the ban isn't lifted—or if the promising early results with fetal tissue don't hold up in the larger studies—researchers are also hedging their bets by exploring other transplant strategies. These include, for example, implanting astrocytes (a type of nonneuronal brain cell) or muscle cells that have been genetically modified to produce the major brain chemicals lost in the degenerative brain diseases. And while this work is still confined to animal models, the researchers say they are encouraged by their results here, too. For now, however, the main clinical focus is on the fetal tissue transplants for Parkinson's disease.

The most dramatic, and convincing, evidence that such transplants can actually help patients comes from Lund, Sweden. At the meeting, Hakan Widner of that city's University Hospital described impressive improvements in two California patients, a man and a woman, who developed a Parkinsonian syndrome after taking a toxic street drug that destroys the same brain neurons as those lost in Parkinson's disease. Those neurons, which are located in the part of the brain that controls voluntary movement, produce a neurotransmitter called dopamine. Ordinarily Parkinson's disease is treated with a drug, called L-dopa, that is converted to dopamine in the brain, helping to make up for the deficiency caused by the nerve cell death. But the male patient, who is in his 40s, and the female patient, who is in her 30s, had developed severe symptoms that L-dopa drug treatment could not relieve.

In treating these patients, the Lund physicians transplanted fetal brain cells from 6- to 8-week-old fetuses. They injected the cells into four sites on each side of the patients' brains; each patient received cells from at least 16 fetuses. Earlier work had shown, Widner says, that fewer cells weren't effective. Positron emission tomography scans performed a year after the transplants showed a dramatic increase in brain dopamine production after the implants, indicating graft survival. More important, the symptoms in both patients were greatly reduced and have remained so for more than 18 months. Although both still require L-dopa treatment, Widner says, they regained the ability "to walk and live an independent life."

Olle Lindvall, also from the University Hospital in Lund, described similar successes with an additional four Parkinson's patients who received fetal tissue implants. "Our data indicate that neuronal grafts can show long-term survival and functional effects," Lindvall told the meeting participants.

The Lund studies are helping to define the conditions under which the transplants

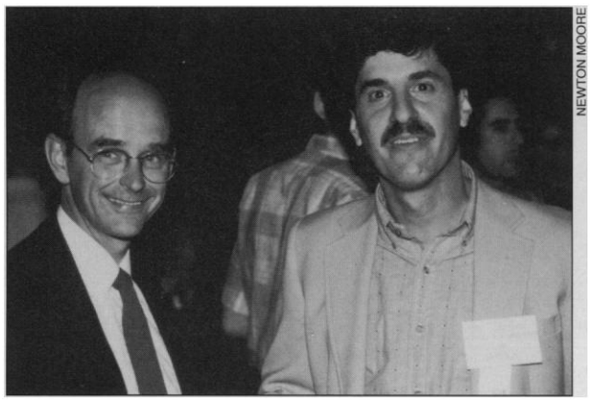
*The meeting was held from 12 to 16 July at the George Washington University School of Medicine in Washington, D.C.

**Results From Fetal Cell Implants in Parkinson's Patients***

| Institution | Number | Results |
|---|---|---|
| University of Lund, Sweden | 6 patients | 4 substantial improvement<br>2 no improvement |
| University of Colorado, Boulder | 7 patients | 4 substantial improvement<br>2 slight improvement<br>1 no improvement |
| Yale University Medical Center, New Haven | 11 patients | Slight improvement<br>One death, of unrelated causes |
| Centro Iberolatinoamericano de Trasplante y Regeneracion del Sistema Nervioso Havana, Cuba | 35 patients | Statistically significant improvement |
| University of Birmingham, England | 12 patients | Temporary improvement in some patients<br>One death |

*As reported at the neural transplant meeting.

work best. In addition to showing, for example, that tissue from a large number of fetuses is needed for good results, they indicate that the implanted cells must be taken from young fetuses, a finding consistent with results from Thomas B. Freeman at the University of South Florida in Tampa. When Freeman implanted human fetal cells into the brains of rats, the Florida surgeon found that the grafts survived poorly if taken from fetuses older than 9 to 10 weeks.



NEWTON MOORE

**Talking it over.** Neural transplant pioneer Anders Björklund *(left)* and meeting co-organizer Jeffrey Rosenstein discuss the results of the latest work.

The need for early tissue may in turn explain why D. Eugene Redmond Jr. of the Yale University School of Medicine found only minimal improvement in 11 Parkinson's patients he treated with fetal grafts. Based on his own studies, done with monkeys, Redmond used tissue from 9- to 11-week-old fetuses. But even though the symptoms of the Yale patients showed some improvement, there was little evidence of long-term graft survival or dopamine production, Redmond says. One patient died, although the death was apparently not related to the treatment. The Yale researcher, who obtained private funding for the study, hopes to continue with younger fetal tissue.

Still, where studies have found improvement, it seems to be long lasting. In the Swedish patients it lasted up to 18 months. And Curt Freed of the University of Colorado Health Sciences Center in Denver, who described the results in seven patients, showed one patient whose improvement had persisted for 45 months. In none of the studies did the Parkinson's patients return to normal, however. What does happen, says Anders Björklund of the University of Lund, is that the implants effectively shift the patients back 5 to 10 years in the progression of their illness to a time when their symptoms can be more readily controlled by L-dopa treatment. It's not clear, however, whether the disease progression has been interrupted permanently or whether the clock has just been reset.

While much of the conference focused on Parkinson's, the participants also reported progress with several other neurological diseases. "Huntington's disease will probably be next" to be treated with implanted nerve cells, predicted Ray Lund from the University of Cambridge, England. Indeed, there already have been scattered reports of individual Huntington's patients, one in Mexico and one in the United States, who received implants and reportedly improved, but those at the conference remain skeptical of the human data (*Science*, 22 November 1991, p. 1108); their optimism about neural transplants for Huntington's patients is based primarily on studies with animal models.

In one such study, Ole Isacson, a Harvard Medical School neurosurgeon, took from rat fetuses the neurons that degenerate in Huntington's (which make the neurotransmitter GABA) and transplanted them into the brains of five baboons whose GABA neurons had been chemically destroyed. Before the treatment, the animals had the uncontrolled movements characteristic of the disease. But within 9 weeks of transplantation, their symptoms had been reduced by half.

Although at the moment fetal tissue may be the most promising avenue of approach to repairing the brain damage caused by neurological diseases, it isn't the only one. Another possibility: packaging dopamine-producing cells from animals such as pigs and cows in plastic capsules having pores that are big enough to let nutrients in and dopamine out, but small enough to keep out immune system components that would otherwise mount an attack on the foreign tissue. Groups from the Massachusetts Institute of Technology, Brown University, and a private biotech company, CytoTherapeutics Inc., of Providence, Rhode Island, among others, have developed systems for encasing different classes of cells in the plastic capsules.

But, aside from fetal tissue, the approach that many researchers consider most promising uses genetic engineering to customize cells from the patient's body so they can compensate for a brain neuron deficiency. "Any [degenerative] disease you can imagine, you can treat by changing protein expression in the cells," said William Freed, head of the National Institute of Mental Health's (NIMH) preclinical neuroscience branch, who organized the conference with Jeffrey Rosenstein of the George Washington University School of Medicine.

For genetic engineering to live up to its promise, however, the researchers first have to find the right cells to manipulate. Some, including Robert E. Strecker of the State University of New York, Stony Brook, have chosen adult astrocytes, the brain's support cells. Astrocytes have several advantages, Strecker says. They are easy to obtain in a biopsy; they divide and grow well in tissue culture; it's easy to insert genes into them; and, once implanted back in the brain, they not only secrete the inserted genes' proteins, they can also induce gene expression in the nerve cells they support. This means that astrocytes might be used, for example, to deliver growth factors that might prevent further neuronal degeneration in diseases such as Parkinson's, Huntington's or Alzheimer's, as well as simpler compounds such as dopamine, Strecker said.

And while muscle cells are less obvious choices for genetic modification than astrocytes, they, too, are showing promise in animal studies. For example, Jaio Shoushu of the University of Wisconsin, Madison, has introduced the tyrosine hydroxylase gene into mouse muscle cells and then transplanted altered cells into mice with experimental Parkinson's disease. Two months later, the muscle cells were producing enough of the missing dopamine to moderate the mouse's symptoms. "We were struck by how consistent and robust the survival of the muscle was in the brain," Shoushu said.

The altered astrocytes and muscle cells are like small drug factories that pump out a chemical the brain needs. But those cells can't reconstruct the brain's primary architecture: the connections among neurons. So another approach researchers are exploring is to put a desired gene directly into the functional cells of the brain. "Instead of having to do a transplant, just change the cell already connected," is how NIMH's Freed describes this strategy.

One potential vehicle for delivering genes straight into neurons is the herpes simplex virus, which naturally infects nerve cells. As a step toward developing herpes simplex virus for eventual use in introducing genes into human brain cells, Joseph Glorioso's team at the University of Pittsburgh Medical School has constructed several hobbled versions of the virus. In animal tests, the altered virus infected nerve cells without causing disease, and genes carried by the virus were active for up to 300 days. But while the work has been promising, Glorioso cautioned, "we are a long way from having the ideal vector." Among other things, he mentioned the need to find the best regulatory sequences for controlling the activity of genes carried by the virus into brain cells.

But even if genetic engineering in the brain is ultimately the more powerful tool, experts at the conference doubted that this high-tech wonder will replace fetal cells any time soon. For now, Widner says, "no alternative cells do what fetal cells do. We hear all the time that there are alternatives that are as good. They are not." And that makes the political roadblocks to this crucial research all the more frustrating to investigators in the field.

**–Larry Thompson**

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