New Fight Over Fetal Tissue Grafts

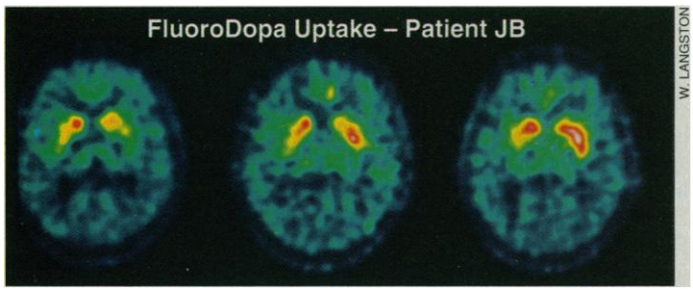
This time it's the researchers, not the politicians, who are arguing over whether a new study of a Parkinson's disease treatment will hurt the field or help it

President Clinton ended a 5-year moratorium on federal funding for research on transplants of fetal tissue a year ago, and many researchers breathed a sigh of relief. The ban had been inspired by anti-abortion activists, and its removal looked like a welcome separation between politics and basic research. But when the National Institutes of Health (NIH) last month awarded its first post-ban grant for a major study using human fetal tissue, the relief for many gave way to gasps of disbelief.

The grant—and immediate cause of that disbelief—was awarded to Curt Freed of the University of Colorado Health Sciences Center to study fetal tissue implants as a treatment for Parkinson's disease. The plan is to transplant fetal tissue that produces the neurotransmitter dopamine into the brains of Parkinson's patients, in the hopes of alleviating the dopamine deficit that afflicts them. Similar implants in the past have produced mixed results. But the new $4.5 million study, funded by NIH's National Institute of Neurological Disorders and Stroke (NINDS) and involving 40 patients, is the largest, most ambitious study of implants to date. Although researchers generally agree that the study is scientifically well designed, many believe it also stands a good chance of crippling the Parkinson's implant research field.

The problem, says Parkinson's researcher John Sladek Jr., chair of the neuroscience department at the Chicago Medical School, is that there are many implant techniques; the Freed study will use just one of them, and if it doesn't work, he says, future funding may be hard to come by. "We legitimize fetal tissue transplants by getting a new president in the White House, and then we put all our eggs in one basket," Sladek laments. "We're worried about what will happen if that basket falls apart."

Sladek is not the only one who's worried. The funding decisions—NINDS declined to sponsor four smaller exploratory studies using alternative techniques—have provoked an outcry among the Parkinson's research community. Hakan Widner, one of the pioneers of fetal tissue transplants at Sweden's University of Lund, brands the funded trial "premature," and signed an unusual letter to *Science* from the Network of European CNS Transplantation and Restoration (NECTAR), "earnestly plead[ing]" with NIH to support other approaches. "What we fear is that this [funded study] will come out as something mediocre, and then become something we have to fight," says Widner.



Grafting hope. Before a fetal tissue transplant, this Parkinson's patient had lower dopaminergic neuron activity *(lighter areas in brain scan at left)*; in the following months, activity increased *(center and right)*.

"Everyone involved in this will have to say the study in 94-95 didn't show anything, but we think we can."

Some critics fault the NINDS peer-review committee that approved the project, arguing that if it knew the field, it would have funded several small studies to evaluate different techniques. Other researchers have attacked the Freed study on ethical grounds, vehemently objecting to a plan to conduct surgery on some control patients without actually giving them tissue transplants.

The man in the center of the storm seems perplexed by the hubbub. "The NIH process is very much single grant oriented, as opposed to a programmatic one," says Freed, who made headlines in 1988 when he used private funding to perform the first fetal tissue transplant on a human in the United States. "[Our grant] is neither the result of a conspiracy nor an endorsement of a single approach."

NINDS officials concur. Acting director Patricia Grady says the institute is "still welcoming" other fetal tissue transplant proposals, and insists that even if the Freed study fails to show that transplants help patients, NIH has no plans to scuttle fetal transplant research. "I would hate to anticipate a negative result," says Grady, "but it would be premature to assume that it would have that kind of an impact."

There have been a variety of experimental techniques used for fetal tissue grafts. Some call for cells from a single fetus, while others use cells from several. Different groups prepare the extracted cells differently. In addition, the cells can be implanted in different regions of the brain. All in all, more than 150 such transplants have been done around the world. But a low percentage of grafted cells typically have survived and improvements in patients, to many observers, have been difficult to objectively prove. Many people outside of the field thus have remained skeptical about reports of dramatic improvements.

The Freed study, which is being done collaboratively with Stanley Fahn of New York's Columbia-Presbyterian Medical Center and Cornell's David Eidelberg, is intended to clear up the ambiguity. The study will treat 20 patients with transplants and use another 20 as untreated controls. To "double-blind" the study, so that neither the patients nor the investigators know who is receiving the transplants, the 20 controls will undergo a sham surgery, in which burr holes are drilled into their heads. This is an attempt to eliminate the placebo effect—the possibility that patients who know they have been treated will improve for psychological, rather than physiological, reasons.

The study does have some support from scientists. "For the first time, some intelligent people are really going to try to prove whether transplantion has something to offer people with Parkinson's disease," says Kris Bankiewicz of Somatix, a California biotech company developing gene therapy treatments for Parkinson's.

Yet many of Freed's colleagues insist that a double-blind trial, though elegant in design, simply isn't warranted now. "The study is an exquisitely well thought out, controlled study," says neurologist William Langston of California's Parkinson Institute. "But we're not ready for a controlled trial yet. I'd like to see some more limited clinical trials." Specifically, the worry is that the optimal techniques have yet to be defined. The University of South Florida's C.W. Olanow, whose own proposal for a smaller study was not funded, explains. "This is not a bitter grapes thing," says Olanow. "It's important to ap-

Fetal Tissue Research on the Rebound

Last month's National Institutes of Health (NIH) award of a grant for a study of fetal tissue implants to treat Parkinson's disease was the first since the ban against such research was lifted in January 1993, but it won't be the last. Parkinson's research is just the tip of the iceberg. NIH officials expect to allocate as much as $5 million in funds for other fetal tissue projects this year.

Fetal tissue's pliant properties—it lives longer than adult tissue in a graft, has low immunogenicity, and is still differentiating into mature cells—have long made it an attractive subject for research into basic developmental biology, and for use as a possible medical therapy in which fetal cells would be transplanted like organs to restore diseased tissue in adult patients. The 1988 ban "really stymied progress," said Delbert Dayton, chief of developmental biology, genetics, and teratology at the National Institute of Child Health and Human Development (NICHD). "It has not allowed this country to pursue the research that we really needed to pursue."

Some of that pent-up demand can now be met. Most of the money for fetal tissue research is being allocated by NICHD, the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Dozens of research teams are vying for a piece of the multimillion-dollar action, and applications are flooding in, according to extramural program managers like Alan Levine, chief of cellular hematology at NHLBI. In addition to Parkinson's treatments, program managers are considering proposals for using implanted neurological fetal tissue in diseases such as Alzheimer's, trauma, stroke, and spinal cord injury; implanting pancreatic islet cells for insulin-dependent diabetes; and grafting hematopoietic stem cells from fetal livers for a host of inherited illnesses, including sickle cell anemia, thalassemia, Fanconi's anemia, and severe combined immune deficiency.

NHLBI has the biggest pot of money for this work, and has committed $1.5 million to fetal tissue trials in the 1994 fiscal year. NIDDK has added another $500,000 to this, for a series of cosponsored studies with the heart institute. Most of this money will go toward studying the transplantation of hematopoietic stem cells from fetal livers into in utero first-trimester fetuses diagnosed with an inherited or acquired illness. In one such study under consideration, a gene coding for a protein that blocks HIV replication would be inserted into fetal stem cells. Those cells would then be injected into the fetus of an HIV-infected woman in the hopes that the treatment would produce immune system cells that can resist infection by the virus.

Because of the fetal tissue's low immunogenicity, "these procedures can be done without the need for tissue matching, without the need for preparative regimens to destroy the recipient's bone marrow, without the need for immunosuppressive drugs to suppress the recipient's immune system so it will not reject the donor...and without graft-verses-host diseases," says NHLBI's Levine. The heart institute has already received more than 30 grant applications for this type of work, but will only be able to support eight, Levine says. The other institutes have not yet determined how many studies they will support, but say that awards could be announced as early as this spring.

–Larry Thompson

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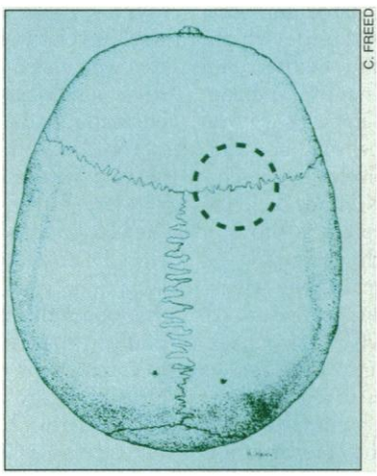
preciate that there are many variables that can influence whether [transplanted] fetal cells survive and whether there is benefit to the patient. Only funding one protocol denies you the opportunity to determine the range of outcomes."

Several researchers have also assailed the ethics of Freed's sham surgeries. "I think that's the most outrageous protocol I've heard of in my life," fumes neurosurgeon Richard Penn of Rush Medical School in Chicago. "We'd all love to do tests like this, but we all do them on our rats." Opening the skull exposes patients to the risks of major surgery but, without the transplants, none of the benefits. France's Marc Peschanski, secretariat of NECTAR, says his country's ethics review boards have expressly forbidden sham surgeries.

Freed counters that the risk of the sham is "vanishingly small" and that the procedure was approved by institutional review boards at all three involved institutions, and it received a green light from NINDS's advisory council. What is more, he emphasizes that the control patients will later be offered transplants through these holes. "No group has thought about these issues more than we have," he says.



Ethical holes. Critics charge the new Parkinson's study involves surgery—through the hole outlined above—with no direct patient benefit.

Ultimately, complaints about Freed's study are being leveled at the peer-review committee at NINDS that evaluated the various proposals. Rush's Penn, speaking for many unfunded researchers who were afraid to criticize this committee publicly, says they were not the group of peers he would have chosen. "As far as I can tell, they didn't have a lot of clinical experience nor were there any eminent neurologists in Parkinson's disease [on the study section that reviewed the grants]," says Penn.

Chicago's Sladek suggests that NINDS's largest failure was that it could have issued a request for applications (RFA) and run a half-dozen different trials simultaneously. "Let's not do this piecemeal," Sladek urges. "Let's do it right. We've been waiting a long time as an academic community and patients have been patient."

But officials at NINDS, as well as Freed himself, don't feel there's much merit to these objections. NINDS's Grady contends that an RFA could have backfired. "We might have limited the responses because an RFA has one response deadline," she says.

And Paul Sheehy, the NINDS scientific review administrator who oversees the study section that evaluated the transplant proposals, flat out rejects complaints about his group's qualifications. Sheehy also emphasizes that, on average, only one in four applications receive NINDS funding. "My impression is that if other investigators can convince their peers that they can dissect out the treatment effect, then their applications would be very well received," he says.

So fetal tissue transplant research, even with the lifting of the ban, remains controversial. But at least now, scientists are framing the debate—and the goal is to benefit patients, not political causes.

–Jon Cohen