Bypassing the Ban

Pressured to abandon their tissue of choice, neuroscientists respond with irritation and ingenuity

By RICK WEISS

The timing was ironic. As 12,000 researchers gathered last month at the Society for Neuroscience's annual meeting, Health and Human Services Secretary Louis W. Sullivan extended indefinitely a ban on federally funded fetal tissue transplants.

The moratorium, which predominantly affects neuroscientists, forbids federal support for experimental transplants of tissue from intentionally aborted fetuses into humans. Continuing a ban initiated in March 1988 by the Reagan administration, it does not apply to transplants of animal fetal cells. Nor does it preclude federal funds for transplanting human fetal cells into animals.

Sullivan, rejecting the conclusions of a National Institutes of Health advisory committee convened last year (SN: 11/5/88, p.296), decided that "permitting the human fetal research at issue will increase the incidence of abortion across the country." The extended ban leaves many neuroscientists complaining that the national debate about the morality of abortion is having too great an impact on the course of scientific investigation.

Although Sullivan's decision irritated many neuroscientists, no one at the annual meeting expressed surprise. Indeed, as if anticipating the extended moratorium, researchers at the Phoenix, Ariz., conference shared a wealth of data from novel experiments in animals — many involving transplants of *nonfetal* nerve cells that may someday find application in humans. While most neuroscientists doubt nonfetal cells will ever match the therapeutic potential of fetal cells, this work stirs excitement among many researchers.

"Even if we find that particular fetal cells have an advantage over postnatal cells, we're becoming very adept at finding out why — and then engineering other cells to do the same thing," says Jean R. Wrathall, a neuroscientist at Georgetown University in Washington, D.C.

Whatever the potential of nonfetal substitutes, fetal cells remain neuroscientists' tissue of choice. Some of those who gathered in Phoenix described experimental transplants of human fetal nerve cells into the brains of animals — experiments many would like to see expanded into clinical trials. A few provided updates on fetal transplants they had performed in humans — either outside the United States or without federal funding.

Although it's too early to tell for sure, some of the experiments indicate fetal tissue may prove valuable in treating Parkinson's disease, Alzheimer's and other neurodegenerative conditions. For example, the first U.S. patient to receive such a transplant — a 52-year-old man with a 20-year history of Parkinson's disease — has responded to his surgery with significant improvements in mobility, reports Curt R. Freed of the University of Colorado School of Medicine in Denver, who performed the surgery with private funds in November 1988.

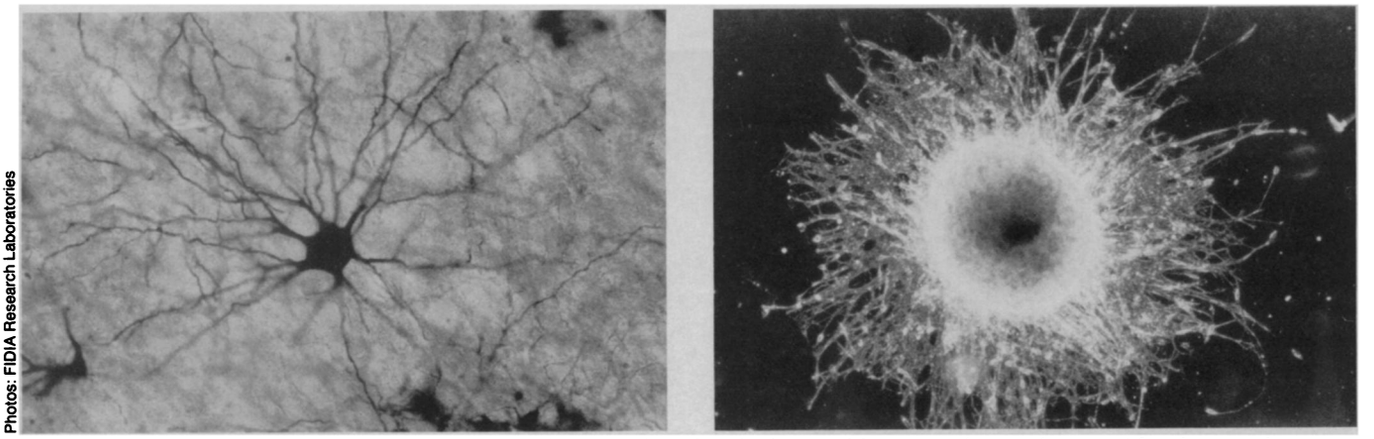
The federal ban undoubtedly will minimize the number of such surgeries in the near future, further delaying any conclusions about the procedure's effectiveness in humans, Freed says. Moreover, the few privately funded U.S. researchers continuing to experiment with human fetal cell transplants complain bitterly about being relegated to the status of scientific renegades.

"We really stuck our necks out," says D. Eugene Redmond, director of the neurobehavior laboratory at Yale University. Nine months after the initial funding ban, Redmond and his colleagues transplanted human fetal cells into the brain of a patient with Parkinson's disease. Since then, the team has performed four more transplants. Each of their transplants has been privately funded.

But while Yale has granted permission for as many as 20 such operations, lack of federal support may prevent Redmond's team from ever reaching that goal. "People think Yale is rich," Redmond says. "But we're continually operating on the brink of not being able to proceed." And with most scientists having better things to do than go scrambling for private contributions for their next fetal transplant, Redmond already sees researchers avoiding such experiments to escape the attendant hassles.

Economic and political problems aren't the only factors prompting neuroscientists to seek alternatives to human fetal cells. "The [funding] problems have in part stimulated people to look for alternatives, but this would have evolved even if there hadn't been a ban on fetal tissues," says Fred H. Gage of the University of California, San Diego. In neuroscience as in all areas of science, he says, "we're expanding our horizons; we're looking for options."

Nonetheless, others say, the political climate has directly influenced many researchers' decisions to pursue nonfetal studies. Redmond notes that scientists have continued to perform experimental transplants of politically noncontentious adrenal tissues into the brains of Parkinson's patients despite largely discouraging results. He cites this as evidence of the abortion issue's powerful influence on current neuroscientific decision making, contending that many researchers have fallen back on the human adrenal



Photos: FIDIA Research Laboratories

Left: Star-shaped astrocytes, which secrete growth-promoting chemicals, provide a nurturing environment for damaged nerve cells, speeding the injured cells' recovery. Right: Cultured nerve cell responds to treatment with a nerve growth factor by sending out an enormous number of new nerve-ending outgrowths.

transplants and other less promising procedures as "a direct result of the political and social controversy" over fetal tissue. "There's no scientist that will tell you they think an adrenal cell is a good substitute for a dopamine-secreting fetal neuron," Redmond says.

Neuroscientist Timothy J. Collier agrees that much of the recent emphasis on nonfetal alternatives has to do with the political climate. However, he laments, "while engineered cells and other cultured cells may be politically convenient, in animal models fetal cells still do the best job of what you want them to do." Last year, in collaboration with Yale researchers, Collier and his colleagues at the University of Rochester (N.Y.) School of Medicine and Dentistry performed the first U.S. transplants of human fetal cells into monkeys' brains. Earlier transplants of monkey fetal cells into the brains of adult monkeys provided some of the first evidence of the procedure's potential usefulness.

Nonfetal cells do show some promise. Just last month, Gage and his colleagues reported they had successfully transplanted genetically engineered rat skin cells called fibroblasts into the brains of rats with a syndrome resembling Parkinson's disease. Engineered to secrete levodopa, a drug commonly prescribed for Parkinson's patients, the cells alleviated the rats' symptoms by an average of 35 percent and may hold potential as a treatment for Parkinson's, say Gage and others. These experiments, described in the November PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (Vol.86, No.22), represent the first time a transplant of genetically engineered cells has induced behavioral changes in animals.

Researchers elsewhere are experimenting with other nonfetal cells – some gene-altered and some not – with equally intriguing preliminary results. For example, many presentations at this year's neuroscience meeting focused on transplants of fibroblasts genetically engineered to produce substances such as nerve growth factor, a protein that stimulates nerve regeneration. These cells, when implanted into the brains of rats suffering from nerve damage, stimulate neuronal repair.

Other researchers have transplanted young astrocytes – star-shaped central nervous system cells – from donor rats onto injured spinal cord tissue in recipient rats. Astrocytes belong to a class called glial cells, which provide physical and biochemical support for neurons. Reports at the neuroscience meeting indicate that transplanted astrocytes and other types of glial cells appear to improve coordination in the injured rats by stimulating the production of nerve-nurturing substances around the injury and by preventing scarring there. Tiny scars can block regenerating neurons from renewing connections with surviving nerve endings.

"It's become a very hot area to look for cells that secrete factors that may facilitate repair," Collier says. "Everyone's very interested in glial cells, which seem to make damaged cells happier."

Researchers have begun genetically engineering glial cells in attempts to enhance their therapeutic potential. However, Freed says, "it will be some time before we become as comfortable with custom-made cells as we are with fetal cells, which we understand much better."

Moreover, scientists have yet to demonstrate that engineered cells can perform all the functions of their fetal counterparts. "I absolutely support [engineered] cell-line research to come up with improved transplant material," Redmond says. "But the probability of taking something like a fibroblast and engineering into it all the factors necessary for neuronal function and communication – so it knows who to talk to, when to release its transmitter – this may involve a thousand things."

Adds Gage: "It certainly is clear that fetal neuronal transplants are more effective than any of the other cell types at present."

Indeed, fetal cells today seem awash in scientific praise. "Their ability to survive and multiply necessitates the grafting of only small numbers of cells; their lower or absent antigenicity eliminates the requirement of tissue matching and immunosuppression; and they are adaptable to the host environment," write University of Rochester neurobiologists John T. Hansen and John R. Sladek in a review article in the Nov. 10 SCIENCE. "The benefits of studying fetal cells are many, and the clinical potential for their use as therapeutic tools is just now being realized," they conclude.

In contrast, Redmond notes, gene-altered fibroblasts and other engineered cells "are going to be extremely suspect" because of their potential to divide uncontrollably, like cancerous tumors. "Some of these alternatives are going to have extreme liabilities."

At this point, says Gage, no one really knows whether fetal cells can live up to their exalted promise. Ban or no ban, he thinks researchers need to conduct more fetal cell transplants into animals – a procedure allowed under the moratorium – before embarking on widespread human trials.

But until the fetal cell transplants into humans can proceed unimpeded, their value will remain an open question, Gage and others contend. And the decision on whether to go ahead with such trials should be based upon scientific rationale, they insist.

"None of the reasons for the ban had anything to do with bad science or good science or whether or not it's reasonable to pursue this work on scientific grounds," Gage says. "I can't believe that patients with degenerative diseases are not up in arms. It doesn't seem real. But then, I'm a scientist." □