Cloud over Parkinson's Therapy

The dramatic improvement claimed for certain Parkinson's disease patients who received transplants of adrenal gland tissue has been questioned

EXACTLY a year ago researchers and clinicians from the Hospital de Especialidades Centro Medico "La Raza," Mexico City reported dramatic improvement in two Parkinson's disease patients who had received transplants of adrenal tissue into their brains. Videotapes of these and other similarly treated patients were so sensational that Ignacio Madrazo, leader of the Mexican team, frequently received enthusiastic acclaim at clinical and scientific meetings. Here, it seemed, was a real breakthrough in Parkinson's disease therapy, the first since the introduction of L-dopa treatment in the late 1960s.

Buoyed by what they had heard on the grapevine, what they read in that first publication, and what they saw at meetings, clinicians in this country were eager to follow suit. By the beginning of July, 29 patients in half a dozen neurology centers in the United States had received grafts of adrenal tissue to their brains. And many of the investigators involved predicted that within 12 months as many as 20 clinical centers would be performing the procedure, with patient numbers exceeding 100.

The dash to the surgical table was the result not only of the promise of unprecedented reduction of symptoms as exemplified by the Mexican experience, but also of the practicality of the procedure. "Any competent neurosurgical team can do this operation," noted John Sladek at a symposium at the University of Rochester midway through last year. However, Sladek, who has been experimentally investigating brain transplant techniques for some years, expressed some unease at the rapidity of the developments.

"There is no question in my mind that people are rushing ahead too quickly," he said. "I can understand why there is so much excitement about the prospects of being involved in this endeavor. But, with laboratory experimentation still at an early stage, the rush to the clinic begins to look premature." Although many neurologists shared Sladek's implicit concern that clinical intervention should be evaluated carefully, fewer believed that the procedure might not live up to its apparent promise.

Nine months later, however, Sladek's caution appears to have been borne out, as revealed at an unusually heated and emotional workshop organized by the United Parkinson Foundation in Chicago at the end of last month. "It was time to assess progress," says Harold Klawans of Rush University, chairman of the workshop. In fact, not only was a timely assessment due, but U.S. investigators were also faced with a major puzzle that had to be resolved. "Although the U.S. results are still preliminary and incomplete, they are clearly not as spectacular as people thought they would be," explains Klawans.

"The disparity between what we see in the American patients and what we have been told about the Mexican patients is substantial."

During the past year Madrazo and his colleagues carried out more than 40 adrenal-to-brain transplants, the great majority of which have been anecdotally represented to be as successful as those in the initial report. Meanwhile, 85 patients were similarly treated in clinics in the United States, the outcomes of which have been disappointing by comparison with Madrazo's results.

"There *is* a beneficial effect in these patients," Klawans told *Science*. "The amount of time they are incapacitated is reduced, and the quality of their 'on-time' is improved." Nevertheless, he adds, "nobody is cured, and all still require medication. The disparity between what we see in the American patients and what we have been told about the Mexican patients is substantial."

Madrazo had been invited to the 2-day workshop, and arrived on the second day. By this time researchers and clinicians present had determined that the Mexican team had a great deal of explaining to do.

For instance, several investigators considered that, judging from the videotapes they had seen, some of the Mexican patients had not suffered from Parkinson's disease but from some other movement disorder. Others reported that patients had come into their care after being operated upon in Mexico, their clinical condition being extremely poor and not at all matching the dramatic improvement typically reported. Still others were concerned that interpretation of results might be difficult because, although patients were held to a strict drug regime postoperatively, it was not at all clear that previous drug therapy had been carefully monitored. And so it went.

"We can't let Madrazo out of here until we challenge him on these things," voiced one participant. The challenge was, by all accounts, vigorous and painful, with little forthcoming in the way of satisfactory explanation. "A disaster," was how one participant characterized it. "Scientific suicide," said another.

In addition to these specific concerns, there is a general frustration among Parkinson's disease investigators because, apart from the initial report a year ago, the Mexican team has published few details of its results. However, Madrazo says that a publication on 30 of the patients is currently being prepared. "We have to be fair to Madrazo," says Anders Björklund of the University of Lund, Sweden. "When we see the full report we may see reasons for the different conclusions."

Klawans is anxious that the reaction to what many see as the collapse of the Mexican data will not be as exaggerated as was the initial enthusiasm. The workshop is scheduled to meet again in November, by which time a better evaluation of the U.S. data will be possible. Meanwhile, many of the groups involved in adrenal-to-brain transplants here are holding off or going ahead only cautiously, awaiting that more thorough evaluation. And several investigators are using this week's meeting of the American Academy of Neurology in Cincinnati to try to collect more data on patients who received transplants in Mexico and are now back in the United States.

The rationale for transplanting pieces of the adrenal medulla into the brain of a Parkinson's disease patient was straightforward and persuasive. The disease is caused

by the specific degeneration of nerve cells in the region of the brain known as the substantia nigra. These cells generate the neurotransmitter dopamine and pump it to another region, the caudate. Until transplant therapy was initiated, standard treatment was daily dosage of L-dopa, which effectively made up the brain's dopamine deficit. L-dopa therapy, effective though it can be initially, is only a holding measure.

The cells of the adrenal medulla produce dopamine. So, properly placed, a small medullary graft was thought to be a potential biological minipump for dopamine, one that might not have the drawbacks of oral delivery. Moreover, the Parkinson's patient could be his own source of adrenal graft material. Following extensive experimental work both here and in Sweden, Björklund and colleagues carried out adrenal grafts in four Parkinson's disease patients in the early 1980s, but with disappointing results. The apparently stunning success of Madrazo and his colleagues in Mexico City 5 years later was therefore a surprise, explicable perhaps by their different surgical approach.

The Rochester meeting of last July included both clinical and experimental data, which together were clearly paradoxical. While the spotlight was shining on the promise of adrenal-to-brain transplants in humans, results from experimental animals appeared to indicate that the approach should at best be rather poor: in most cases the grafted cells simply did not survive. Indeed, the results from adrenal transplants in experimental animals had been so discouraging that most researchers had turned—or had maintained—their attention to transplanting nerve cells into the brain.

The rationale of brain-to-brain transplantation is obvious: replace what is missing in the diseased brain and you surely have a good chance effecting some degree of repair. In fact, investigation into brain transplantation has a long history, going back to the 1890s. Recently, however, interest has been booming, and the latest discussion of prospects for the technique took place at the Massachusetts Institute of Technology (MIT) earlier this month.

In addition to addressing the four basic questions of brain transplantation—namely, do the cells survive; grow normally in size and shape; extend dentrites and axons into the host brain; and make appropriate synaptic connections?—the MIT meeting also explored various avenues of producing nerve cells in culture that might serve as graft material. Such a development would obviate the obvious ethical issues involved in obtaining and using nerve cells from human fetuses as transplant material (see box).

By the time of the Rochester meeting last

Ethical Issues Raised

Just a few days before Massachusetts Institute of Technology hosted a scientific meeting on "The biological basis of brain transplants," the Reagan Administration banned the National Institutes of Health (NIH) from using fetal tissue from induced abortions in transplantation procedures. The decision, which was made as a result of an NIH proposal to explore the use of human fetal material in Parkinson's disease therapy, is certain to slow down development in this promising but highly sensitive area of research. "This proposal raises a number of questions—primarily ethical and legal—that have not been satisfactorily addressed, either within the Public Health Service or within society," Robert E. Windom, assistant secretary of health at the Department of Health and Human Services, wrote to NIH director James B. Wyngaarden. The NIH has been directed to establish an outside advisory committee to examine the various ethical and legal issues involved in the medical use of fetuses from induced abortions—the subject of the new ban—and to include consideration of current practices governing use of tissues from spontaneous abortions and stillbirths.

The use of human fetal tissue for experimental research is tightly circumscribed in the United States by both federal and state regulations, the result of specific legal cases and legislation. The prospect of using fetal material in therapeutic procedures—and particularly brain-to-brain transplantation—extends the ethical and legal issues even further than previously has been contemplated. As a result of the growing practical feasibility of this kind of approach during recent years, investigators and ethicists have been trying to grapple with the problem.

For instance, in noting that "transplantation of fetal tissue holds the promise of great benefit to victims of serious neurological disorders," participants at a meeting at Case Western Reserve University a little over a year ago concluded that "retrieval of such tissue from fetal remains is analogous to the transplantation of organs or tissue obtained from adult human cadavers." Differences were acknowledged, however, and a series of conditions proposed, which were: "1. a clear separation between decisions related to the acquisition of tissue and decisions regarding the transplantation of tissues into a recipient; 2. anonymity between donor and recipient, with the implication that donors and recipients should not be filial relations; and 3. adequate input from knowledgeable experts concerning the soundness of the research design and the assessment of risks to human subjects."

According to current law, the use of nonviable, spontaneously aborted fetuses could be considered for therapeutic transplantation. However, such a source is neither large nor reliable, given the careful planning required for successful surgery and the very large number of potential patients who might benefit from nerve cell transplants. The very great sensitivity surrounding induced abortion, which would provide a more reliable and larger supply of potential transplant material, makes this road an uncertain one to try to travel. But, notes LeRoy Walters of Georgetown University, perhaps transplantation of fetal brains raises ethical issues that do not have practical solutions. "Is brain tissue uniquely identified with a particular individual? Do we violate an important interpersonal barrier if we transplant brain tissue from one individual to another, even for such a laudable goal as treating Parkinson's disease?"

In general, objection to the use of fetal tissue in transplantation therapy can take the form of the "slippery-slope" argument, says Mary Mahowald of the Center for Biomedical Ethics, Case Western Reserve University. "This argument is valid and relevant, but neither more nor less compelling here than is the slippery-slope reasoning with regard to issues such as the permissibility of abortion (leading to infanticide) or withdrawl of life-sustaining treatment (leading to euthanasia)." All ethical decisions tend to be difficult, with no clear-cut lines to act as an objective guide. "Accordingly, if transplantation of fetal tissue is permitted, reliable checks must ensure against extending the technique to living, viable individuals, and against commercialization that would trivialize human life in its nonviable stage." ■ **R.L.**

ADDITIONAL READING

M. B. Mahowald *et al.*, "Transplantation of neural tissue from fetuses," letter to *Science* **235**, 1307 (1987).

L. Walters, "Ethical issues in fetal research," *Clin. Res.* **36**, 209 (1988).

year it was already clear from laboratory work that transplanted nerve cells could indeed survive in host brains and could repair experimentally induced deficits, including symptoms of Parkinson's disease. At MIT last week Sladek described further encouraging work in monkeys and Björklund reported new results on rat transplants.

The work with monkeys, which Sladek does in collaboration with Eugene Redmond and Robert Roth of Yale University, is a close model of Parkinson's disease, and forms a strong rationale for going ahead with nerve cell transplantation in humans. Symptoms of the disease are induced in the animals by dosing them with a chemical known as MPTP, which specifically destroys cells of the substantia nigra. The Rochester and Yale researchers have shown that substantial functional recovery can be achieved by transplanting monkey fetal nigral cells into the caudate region of the host brain.

The animals began to recover within a few weeks of the operation and in most cases continued to do so for at least 7 months. "Recovery correlates well with graft survival and the elevation of dopamine metabolites," says Sladek. It is now clear too that the graft cells send fibers into the host brain, but the nature of synapses—if any—they make remains to be established. The effect appears to be specific, in that an animal in which cells from the cerebellum were placed in the caudate did not recover. Neither did an animal in which nigral cells were transplanted into the cortex. And, interestingly, nor did these nigral cells send fibers into the surrounding tissue to anything like the extent of the transplant in the "right" place.

In fact, the right place for transplanting nigral cells would, of course, be the substantia nigra, not the caudate. The rationale for placing the cells in the caudate is that this is the "target" of the dopamine from the substantia nigra, which gets there via long axonal connections between the two areas. "It is more difficult to get at the substantia nigra because you have to go through brain stem areas," says Sladek. "It would be possible to get there using stereotactic techniques for injecting cell suspensions, but the caudate is certainly the easier route."

In any case, as Björklund notes, placing nigral cells in the caudate might be efficacious because "the cells appear to be under rather slow, general control: specific connections might not be necessary." Based on this and his own work, Björklund and his colleagues have recently performed transplants of human fetal nigral cells into two Parkinson's disease patients. "We will be making an assessment of their progress at 6 months after the procedure, which will be in June," he told *Science*.

More specific repair of neuronal connections might be necessary in other conditions, such as Huntington's disease, for which Björklund and his colleague Klas Wictorin have an elegant animal model. Following chemically induced damage in the striatum of rats, Wictorin and Björklund transplant fetal striatal cells and find quite remarkable results. "Not only do you find the neurotransmitters you would expect, such as GAMA and acetylcholine," says Björklund, "but you also find that the graft makes and receives appropriate connections with neighboring areas."

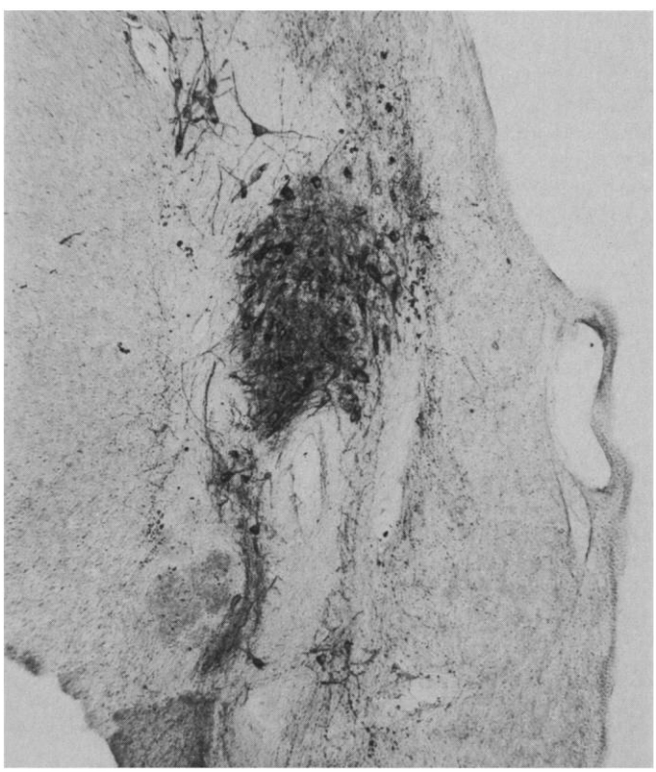
So far no other group has demonstrated such specific repair via nerve cell transplantation. "Extraordinary," says Sladek. "Quite the best work there is." For the growing fibers of transplanted cells to be able to find their way to appropriate brain areas, and make functional connections there, it appears necessary that the host brain is physically damaged to some extent. Presumably, the interacting cells are then replaying whatever information systems operate in the developing embryonic brain. In any case, these results give some encouragement that specific repairs can be effected in some brain diseases.

Although the time "window" during which human fetal brain cells can usefully be transplanted is wider than was inferred from rodent data, there are many obvious problems with employing this material. If cell lines can be developed from human fetal brains, then these problems can at least be diminished to some extent. Researchers at Hana Biologics Inc. of Berkeley are pursing this approach, and, working with pig brains, so far have managed to get an 80-fold proliferation of cell number by culturing tissue through two "passages." Beyond two passages, the cells begin to differentiate, at which point they are difficult to remove from culture without damaging them.

Hana's Ray Miao is cautious about the notion of establishing immortal cell lines, an approach favored by some investigators, "because there is a high probability that the cells will be abnormal." Tumors grow very rapidly in the brain, and so transplanting any tissue that might proliferate without control is a significant safety issue.

More speculative is the idea of tailoring cells to clinical requirements. For instance, as Paul Patterson of the California Institute of Technology reported at the MIT meeting, it is possible under the correct conditions to culture cells of the adrenal medulla and produce an array of precursor nerve cells that could be used in transplants for Parkinson's and Huntington's disease. Medullary cells are embryologically derived from nerve cell precursors, and are therefore amenable to this kind of manipulation.

So, a year after the first rush of enthusiasm, the prospects for repairing some diseases of the brain are perhaps dimmer in the short term but certainly brighter in the long term. ■ ROGER LEWIN



Growing graft

A graft of monkey fetal nigral tissue is seen in the center, surviving in the caudate nucleus after 7 months, with a group of fibers growing out (downwards here) into the host brain. [*Courtesy of J. R. Sladek, D. E. Redmond, Jr., R. H. Roth, and colleagues (unpublished)*].