Dramatic Results with Brain Grafts

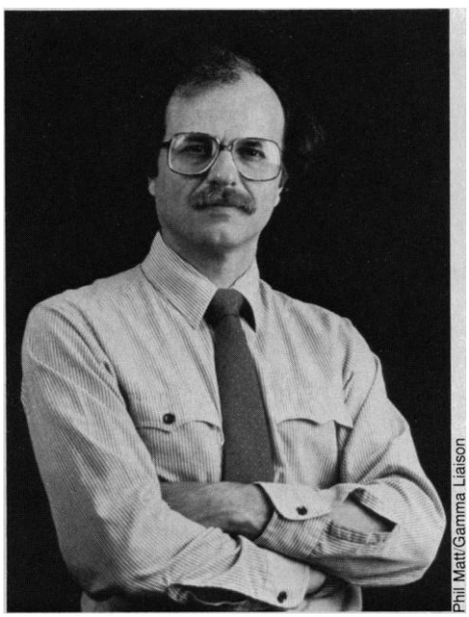
The repair of disease through tissue implantation into the human brain is a revolutionary medical concept, but one that is already beginning to show some promise, specifically with Parkinson's disease

BARELY 3 months ago a team of neurologists in Mexico City reported what appeared to be the first successful treatment of Parkinson's disease in which adrenal tissue was implanted into the brain. Since then, four neurology centers in the United States have followed suit—the most recent being last week at New York University Medical Center—bringing the total number of such implant patients in North America to 29. Within 12 months another 15 U.S. hospitals are expected to have announced that they too have joined the list.

"Any competent neurosurgical team can do this operation," notes John Sladek of the University of Rochester Medical Center. "But there is no question in my mind that people are rushing ahead too quickly. I can understand why there is so much excitement about the prospects of being involved in this endeavor. But, with laboratory experimentation still at a very early and uncertain stage, the rush to the clinic begins to look premature." For instance, more humans have now undergone the adrenal implant procedure in the clinic than monkeys have experimentally in the laboratory.

The prospect of repairing specific neurological defects with tissue implants into the brain, rather than drug therapy, is a revolutionary and heady notion, and was the subject of a recent meeting* organized at the University of Rochester. Although the meeting was originally designed to address the basic cellular, physiological, and immunological aspects of implanting foreign tissue into brains, and included attention to diseases such as Alzheimer's and Huntington's, there was no question that the recent developments with Parkinson's disease stole the show.

The centerpiece was a presentation by Rene Drucker-Colin, of the Hospital de Especialidades Centro Medico "La Raza," Mexico City, who showed a videotape of some of his implant patients before and after surgery. Although none of the patients was restored to normal after the procedure, one man who had been rendered virtually immobile by the disease eventually became well enough to return to his home, where he ran a small farm. Others showed degrees of recovery almost as dramatic.



Phil Matt/Gamma Liaison

John Sladek: *"With laboratory experimentation still at a very early and uncertain stage, the rush to the clinic begins to look premature."*

The intensity of applause at the close of the presentation demonstrated the admiration that much of the audience felt for Drucker-Colin and his pioneering Mexican colleagues. In addition to research neuroscientists, the audience included large numbers of neurosurgeons who had come to Rochester specifically to assess the prospects of doing the implant operation themselves. As a result, the overall response to the presentation was somewhat ambivalent. Many of the neurosurgeons apparently felt, "it works, so let's get on with it." By contrast, many of the research neuroscientists were more cautious, saying, "it's not clear what's going on here, so let's get some more information."

There is no doubt that the situation is far from straightforward, not least because no one can be certain what exactly was responsible for the apparent improvement in the Mexican patients. Moreover, the one group in the United States with most experience with this therapy—George Allen's at Vanderbilt University Medical Center—has so far produced results that are far from dramatic. "We see change in the direction of improvement," Allen reported at the Rochester meeting, "but it is too early to make any definitive statements."

Parkinsonism is one of the most common neurological diseases, and affects upwards of 1 million people in the United States, most of whom are over the age of 60. The disease appears to be caused principally by the degeneration of a group of cells in an area of the midbrain called the substantia nigra, the result of which is a series of movement disorders, including tremors and rigidity.

The cells of the substantia nigra send fibers to higher centers, known generally as the striatum, where they pump out the neurotransmitter dopamine. It appears to be the loss of dopamine that causes the movement disorders, although the precise functional explanation for it is still a mystery. Most—but not all—Parkinson's patients therefore benefit dramatically from the administration of the drug L-dopa, which effectively substitutes for the brain's missing dopamine. This form of therapy was introduced in the late 1960s and, until quite recently, has virtually dominated therapy and research in the disease.

The problem with L-dopa therapy, however, is that over a period of 5 to 10 years most patients progressively fail to respond, and in some people it eventually causes severe convulsions and hallucinations. This decline in a patient's beneficial response to L-dopa appears to be due in part to a progressively adverse physiological reaction to the drug itself, but also to the continued degeneration of cells in the substantia nigra. For this reason a large clinical trial was recently launched that will test the effect of certain drugs in slowing down the degeneration of the cells of the substantia nigra

*The "Schmitt Neurological Sciences Symposium" was held in Rochester, New York, 30 June to 3 July.

(*Science*, 12 June, page 1420).

Ira Shoulson of the University of Rochester described the 5-year, $10 million trial as "a potentially new approach to treating Parkinson's disease, that of protecting the nigral neurons." The drugs being tested, both separately and in combination, are Deprenyl, which blocks the enzyme monoamine oxidase, and tocopherol, which is a general antioxidant. The rationale for testing Deprenyl is that recent research has implicated some kind of environmental toxin in the destruction of cells of the substantia nigra, a process that might well be speeded up by monoamine oxidase. Tocopherol, a form of vitamin E, might be beneficial through mopping up harmful oxidative radicals, produced perhaps from external agents or by enhanced enzymic action on natural neurotransmitters.

Meanwhile, the idea of implanting a dopamine-producing tissue into the brain in an attempt to target specifically the deficit in the substantia nigra has long been contemplated as a possible alternative to L-dopa therapy. The obvious tissue to use would be substantia nigra cells themselves, because this would be replacing like with like. By 1979, rats with experimentally induced parkinsonism were shown to be significantly improved by an implant of nigral cells into the caudate nucleus of their brains.

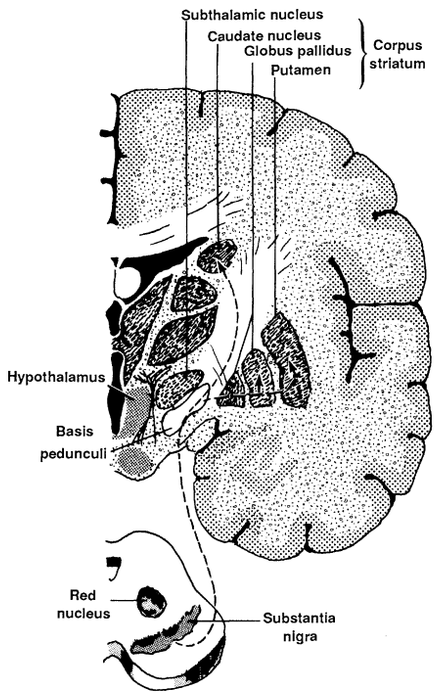
However, because of the problems associated with obtaining suitable human nigral cell implants—which must come from early fetuses—attention switched to using adrenal tissue, for which the Parkinson's patient could be his own donor. The central part of adrenal glands—the medulla—produces dopamine, among other things. A medullary implant into the caudate can therefore be seen as a dopamine pump right at the site where the neurotransmitter is required.

Although adrenal implants in experimental, parkinsonian rats were not particularly encouraging, Anders Bjorklund and his colleagues at the University of Lund, Sweden, tried the procedure in four Parkinson's patients in 1982. The results were disappointing at best, and the group has since turned its attention back to the prospects of fetal nigral implantation. Certainly, this was the principal experimental focus of presentations to the Rochester meeting, where eight reports described fetal nigral implants in rats and various nonhuman primates and only one described adrenal implants in nonhuman primates.

Comparison of results of implants described at the Rochester meeting and of those already in the literature was clear-cut. "Animal studies show that some of the fetal nigral implants look good in rats and monkeys," says Stanley Fahn of the Neurology Institute, New York. "They look definitely better than adrenal medullary implants. One would not have predicted from these kinds of results that the adrenal implants in humans would have done so well."

The one direct comparison of the efficacy of adrenal as opposed to fetal nigral implantation was described by Krzysztof Bankiewicz and his colleagues at the National Institutes of Health (NIH). These workers used rhesus monkeys that had been rendered parkinsonian by the specific brain toxin known as MPTP, the chemical that has helped ignite a revolution in Parkinson's disease research in recent years.

Although the animal with the adrenal implant recovered somewhat after the surgery, the beneficial effects were short-lived, even though the graft itself was still viable and pumping out dopamine up to 6 months after being implanted. By contrast, the fetal implant appeared to bestow a strong and continued recovery. And, not only was the graft still alive at 7 months, but it had sent out a cloud of newly sprouted fibers into the surrounding tissue.



Dopamine path: *Cells of the substantia nigra, which pump dopamine to the striatum via long connecting fibers, degenerate during the aging process, sometimes causing Parkinson's disease.*

Because both the adrenal and fetal nigral implants were still viable and producing dopamine after at least half a year, and yet only the animal with the nigral implant showed any sustained recovery, Bankiewicz concludes that "the recovery from the parkinsonian condition is not dependent on the presence of a mini-pump for dopamine."

In a more extensive study of fetal nigral implants in nonhuman primates—this time on African Green monkeys—Sladek and his colleagues at Rochester joined forces with Eugene Redmond at Yale University, and now have results on 14 animals. "We were asking four questions," said Sladek. "These are: One, do the graft cells last in the host brain? Two, is there evidence for integration of the graft cells with the host brain? Three, is recovery dependent on dopamine? And four, do the grafts promote recovery from the parkinsonian state?"

Some of the monkeys were monitored for as long as 7.5 months after the implants were put in place, and the results look very encouraging. Yes, a good proportion of the implant cells do survive. Yes, the implant cells appear to become integrated with the host brain, sending out clouds of fibers, just as the NIH group had seen. Yes, there are elevated levels of dopamine in and around the graft area. And yes, there is good, sustained recovery in nigral implanted animals (but not in a control, in which cells from the cerebellum were substituted for those from the substantia nigra). "There was good correlation between the biochemical, physiological, histological, and behavioral measures," noted Sladek. The contradictory conclusions over the apparent role of dopamine in the nigral grafts between the NIH and Rochester groups has yet to be resolved.

It is perhaps not surprising that fetal nerve cells would survive and sprout new fibers in a favorable environment, but a key issue is whether the sprouting is specific or random. Although this question cannot yet be answered definitively, there are a number of reports of somewhat anecdotal evidence that the graft cell fibers are projecting to appropriate rather than inappropriate neighboring centers. "This gives an impression of specificity," suggests Sladek.

It was against this background of a heavy emphasis on nigral rather than adrenal implants that Drucker-Colin presented the impressive Mexican results. "We decided to try adrenal implants, in spite of the Swedish group's failure with them, because we thought we could put the implant in a more favorable location," he reported. "The Swedish group had injected suspensions of medullary cells deep into the striatum. We decided to place pieces of medulla on the surface of the caudate nucleus, where they would be bathed in cerebrospinal fluid." There had been real concern in the Swedish procedure that the adrenal cells, buried as they were, would be unable to survive. Being exposed to the cerebrospinal fluid might help sustain them, it was thought. "It seems to have worked," said Drucker-Colin.

In addition, Shou-shu Jiao, of the Capital Institute of Medicine, Beijing, also showed videotapes and reported on three parkinsonian patients who had been treated with adrenal implants. Like some of the Mexican cases, these Chinese patients had been rendered virtually immobile by the disease, and they too responded significantly, if not completely, to the treatment.

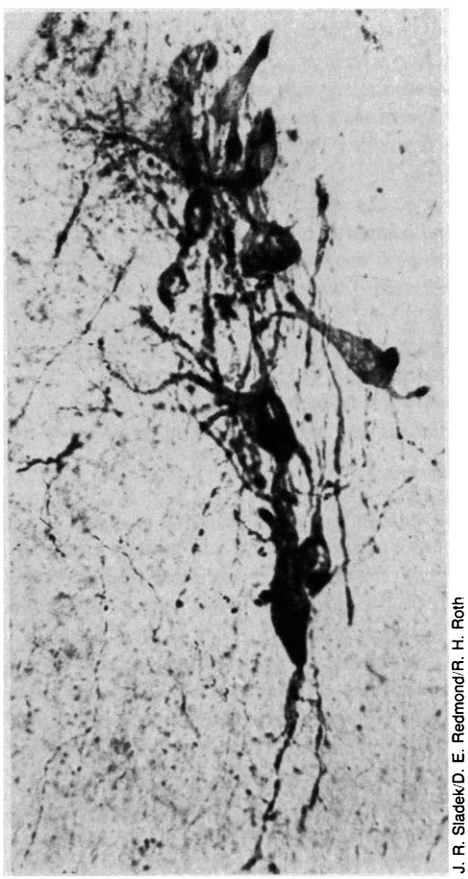
"There's no doubt that the patients improved dramatically," observed Abraham Lieberman of New York University Medical Center, "but it is not at all clear that the improvement is the result of dopamine produced by the implant. My guess is that you are doing something more fundamental than anything I can do by putting a little dopamine into the brain. But I have no proof." It is true that the Mexican group was unable to show any sign of increased dopamine levels in the cerebrospinal fluid. And Allen's group at Vanderbilt University also failed to detect elevated dopamine in the brains of patients who had implants.

"The first thing you have to eliminate is some kind of surgical effect," says Sladek. "The neurology literature is filled with reports from the fifties and sixties that surgical interruption of several different sites in the brain could alleviate some of the signs of parkinsonism." One popular explanation at the Rochester meeting was that the improvement was the result of the release of trophic factors—produced either by the graft itself or by the effect of surgery on the patient's brain—that stimulated the previously faltering nigro striatal system. "It's an attractive hypothesis," Allen told *Science*.

The untimely death of one of the Mexican patients—3 of 18 have died so far—seemed to provide some insight into this debate. Drucker-Colin showed slides of the implant area in a patient who had died of heart failure 43 days after surgery. "As far as I could see, none of the adrenal cells appeared to be viable," says Don Gash of the University of Rochester. "The graft seemed to be full of macrophages." Gash told *Science* that the large size of the graft had surprised him, as had the degree of surgical trauma in the patient's brain.

Here then was a patient who, according to Drucker-Colin, had been recovering from his parkinsonian symptoms right up to the time of his death, and yet whose implant was apparently not surviving. "This seems to indicate that it was something other than a normally functioning graft that was responsible for recovery from symptoms," says Gash.

Whatever is responsible for the dramatic recovery of the Mexican patients, some of whom had their implant more than a year ago, there is no doubt that the Mexican experience has stimulated others to try the same procedure, in spite of the lack of experimental backing. So far Allen's group has operated on 6 patients, and has permission for 12 others. The patients will be in one of three groups, according to their age and the severity of the disease. "We hope to get a careful, scientific assessment of the procedure," says Allen. "We want to test the hypothesis, prompted by the Mexican work, that adrenal medulla placed in the surface of the caudate and in contact with cerebrospinal fluid would alleviate the parkinsonian symptoms. We wanted to head off 50 groups all over the country going ahead and each just doing a few patients." Too late, it seems.



J. R. Sladek/D. E. Redmond/R. H. Roth

Brain graft. *The photomicrograph shows fetal nigral cells that have been implanted into the striatum of an experimentally induced, parkinsonian African Green monkey. The implanted cells are sending out a cloud of new fibers into the host brain tissue.*

Impressed though many people were with the Mexican results, the caution emanating from the Vanderbilt experience clearly had an impact too. In any case, there is now great interest in the outcome of the first fetal nerve cell implant in humans, which will be done by Bjorklund and his colleagues in Sweden within the next 12 months. These researchers have been implanting human fetal nigral cells into experimental rats, addressing questions such as the optimum age of the graft at implant and the size of graft required. "My guess is that their grafts will be successful," says Sladek. "They are doing a great deal of basic research and are translating it into a meaningful approach to human patients."

Although the results of the first human fetal nigral cell implant are eagerly awaited, there is also a degree of apprehension about the approach. "Putting aside the practical and ethical problems of getting appropriate donor tissue," comments Allen, "there is the issue of graft rejection. We've seen signs of rejection in some experimental animals, and we don't know what this would mean in functional terms in humans." Presumably, long-term immunosuppression would be necessary, he suggests. Bjorklund points out, however, that the brain is somewhat protected from the immune system, and nigral transplantation within species should not provoke a clinical rejection. Allen notes another potential issue. "We don't know what fetal tissue would do over a period of many years," he says. "There's a possibility it could grow and become an invasive tumor."

These concerns were repeatedly expressed in comparing the adrenal versus fetal brain approach. But implanting a patient's own adrenal medullary tissue into the brain has its problems, not the least of which is ensuring that the implant does not include cells from the outer, cortical layer of the gland. "It is very difficult to ensure you don't accidentally include cortical cells in a medullary graft," says Gash, "especially when the procedure is done as rapidly as it must be during the implant operation. Cortical cells produce adrenocorticosteroids, and who knows what effect there would be of bathing the brain with these substances."

A good deal of research attention is now turning to the development of alternative implant tissue, such as specially cultured cell lines and even genetically engineered cells. Such an approach might eventually overcome the several dangers currently inherent in using a patient's own adrenal tissue or foreign fetal brain tissue.

"The effect of all this dramatic progress goes way beyond Parkinson's disease," observed Lieberman. "This was a seminal meeting, and you can see potential for many other diseases, including Alzheimer's disease. Until now, neurology has told us that if you damage the brain, that's it. We'll teach you how to compensate for this. Maybe we'll give you a chemical to replace what you've lost. But this is the first time we've said, look, if you damage your brain, there might be a way to repair it. That's remarkable." ■ **Roger Lewin**