Brain Grafts Benefit Parkinson's Patients

Two Parkinson's disease patients in Mexico City apparently showed dramatic improvement in movement, speech, and other symptoms after receiving transplants from their own adrenals

Just a little over a year ago Ignacio Madrazo and his colleagues at La Raza Hospital, Mexico City, removed the right adrenal gland from a 35-year-old man suffering from Parkinson's disease and transplanted part of the gland—the medulla—to the patient's brain. The hope was that the adrenal tissue would manufacture the neurotransmitter dopamine, the absence of which was the cause of the parkinsonism. When, the following November, Madrazo reported at the Society for Neuroscience annual meeting in Washington, D.C., that the transplant had produced "an excellent degree of amelioration of most clinical signs of Parkinson's disease," there was near universal skepticism and incredulity. One reason for the skepticism was that 2 years previously a group of Swedish researchers tried a similar technique, with virtually no improvement in their patients' condition.

The Mexican team has now published the case in the the current issue of the *New England Journal of Medicine*, and have included the description of a second successful patient, this one a 39-year-old man. In both cases, according to the clinical descriptions, these previously incapacitated patients enjoyed dramatic and continued improvement, with the abolition of tremors, speech impairments, and movement disorders. Faced with this new evidence, observers are still incredulous but recognize that they must take it very seriously. "Either these results are erroneous in some way, or they are real and dramatic," says Curt Freed of the University of Colorado. "There is no reason to question the integrity of the scientists."

"One problem is that the results seem to be *too* good," comments William Freed of St. Elizabeths Hospital, Washington, D.C. He is refering to the fact that although the transplants were done to just one side of the brain—the right side—the patients appear to have improved on both sides of their body. This is not easy to explain.

Parkinson's disease results from the degeneration of certain dopamine-producing cells in two separate networks of nerves, one on each side of the brain. Traditional treatment has involved taking the drug L-dopa, which alleviates the deficit of dopamine but is rarely satisfactory in the long term. Transplant therapy has been seen as potentially a more "natural" and therefore more powerful therapy—if it works.

By now more than half a dozen laboratories in this country have been working with animal systems in exploring the prospects of transplant therapy, using rats, mice, and monkeys. Some of them are transplanting tissue from the substantia nigra—which is the area that degenerates in Parkinson's disease—taken from fetuses. This approach has the benefit of replacing the degenerated tissue with the same type, but would face obvious ethical problems in human therapy. Other groups are trying tissue from the adrenal medulla, which does produce dopamine but may not match the needs of the brain. Nevertheless, a patient can give an adrenal transplant to himself—as in the Mexican cases—and therefore avoid ethical and immunological problems.

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The Swedish attempts at transplant therapy involved mincing adrenal medullary tissue and injecting it via fine needles into the caudate nucleus, which is part of the dopamine-producing system in the brain but at the opposite end from the substantia nigra. As experiments using a similar technique on animals have confirmed, adrenal cells that are injected deep into the caudate appear to die off rapidly. By contrast, adrenal tissue that is placed on top of the caudate nucleus—and is bathed in the cerebrospinal fluid (CSF) in the surrounding ventricle—usually survives. As William Freed notes, "The Mexican group took careful note of these experimental results, and did their transplants accordingly."

If the location of the transplant—on top of, not deep within, the caudate—explains the survival of the adrenal tissue in the Mexican patients, how is the beneficial effect to both sides of the brain to be explained when the transplant was made to just one side? Madrazo and his colleagues are unsure, but suggest that it results from "the release of dopamine into the ventricles, from which it would then reach the contralateral caudate." Robert Moore of the State University of New York at Stony Brook is unconvinced by this idea. "The amount of dopamine produced is small," he says. "The degree of diffusion away from the caudate is great. And the amount of penetration of dopamine into the caudate from the CSF would be small."

His suggestion is that, instead of providing a source of dopamine, the transplant could be releasing growth factors that stimulate the remaining nerve tissue to proliferate, thus making up the deficit that way. There is some support for this idea in experimental work on mice by his SUNY colleague Martha Bohn.

If this interpretation is correct then it has implications for the potential efficacy of transplant therapy in the typical population of parkinsonian patients. The progression of the disease involves continued degeneration of the substantia nigra and related areas. Patients with advanced disease might therefore have very little nigra left to respond to the growth-promoting factors from the transplant. And even those patients who do respond might simply be delaying rather than preventing further degeneration. It is interesting that the dramatic beneficial effects that Madrazo observes are in unusually young patients, whose neuronal degeneration might not be very advanced.

No brain transplants for Parkinson's disease patients have been reported yet in this country, but some are likely soon. In an editorial in the same issue of the *New England Journal of Medicine*, Moore suggests that the National Institutes of Health should initiate a clinical trial on transplants in order to establish the validity of the effect reported by the Mexican researchers.

Meanwhile, researchers are continuing with animal experimentation and are due collectively to report their latest results at a meeting at the University of Rochester at the end of June. So far the results are said to be encouraging, both with nerve and adrenal tissue transplants, but none of them appears to record a degree of improvement as dramatic as occurred in the Mexican patients. "This is a very exciting time," says William Freed, "but we have to try to evaluate the results as dispassionately as possible." ■ **Roger Lewin**