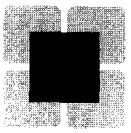

CNS transplantation: a treatment for Parkinson's disease?

THE FIRST human autologous transplantation procedures to treat Parkinson's disease, reported in 1981 from the Karolinska Institute in Sweden, only transiently caught the interest of the medical community. The reports were scarcely mentioned in the popular press. However, the growing number of adrenal gland-to-caudate nucleus transplantations performed over the last two years, first in Mexico and later in other countries, including the United States, has kindled a great deal of interest not only in the medical community but with the general public.

Does transplantation hold promise for the estimated 500,000 U.S. patients with the malady James Parkinson referred to as "the shaking palsy"? This brief overview discusses the experience with transplantation procedures to date.

■ *See Korfali et al (pp 259–262)*

CNS transplantation attempts on laboratory animals date back to the latter part of the 19th century. The earliest efforts reported, in 1890, attempted to transplant pieces of cerebral cortex from adult cats to adult dogs.[1] None of these attempts were successful until 13 years later when, in 1903, transplants using immature fetal tissue were carried out. For the first time, using fetal rather than mature tissue, neurons survived up to three months after surgery. By 1940, the importance of immature tissue, with a rich source of blood supply to ensure transplant "take," had been confirmed by repeated experiments.

In 1971, Das[1] established unequivocally that transplanted immature neurons can survive and mature, and the age of the recipient animal had less bearing on survival of the transplanted tissue. Immunological rejection of the grafted tissue was not as much of a problem as rejection elsewhere in the body because of the immunologically "privileged" status of the CNS.

The 1981 Swedish experience with human transplantation for Parkinson's disease involved mincing parts of the patient's adrenal medullary tissue and then injecting it, via fine needles, into the depths of the caudate nucleus. The lack of success with this method related to the failure of the adrenal cells to survive.[2] In the newer Mexican technique, however, the patient's adrenal tissue was placed in a surgically prepared bed on the surface of the caudate where, in this superficial position, it was bathed in the surrounding cerebrospinal fluid. Just how this unilateral procedure resulted in alleged bilateral benefit was not entirely clear. One theory suggested that the released dopamine diffused in the cerebrospinal fluid to the contralateral side. Another suggested that the transplant actually released unidentified "growth factors," which stimulated the remaining nerve tissue to proliferate and produce dopamine.

Sladek and Shoulson[3] suggest that improvement in signs and symptoms might be produced by even a small amount of injury and subsequent inflammation of the caudate such as might be had with the cavitation procedure itself for the adrenal block attachment. This would explain an observation made over four decades ago when Meyers[4] reported transient and variable improvement in Parkinson's disease patients who had undergone neurosurgical extirpation and sectioning of the caudate and the immediately surrounding brain regions. Riopelle[5] has suggested that it is not so much the graft itself but rather the surgical trauma and injury to the caudate that stimulate remaining cells to release trophic neuronal growth factors.

Since these early reports from Mexico, several hundred adrenal graft procedures have been performed worldwide, many of them in China. Coincident with

these operations, however, has been a number of vexing questions. For example, not all of the transplant patients have been comparable in terms of age and state of disease progression. Thus, should patients undergo transplantation earlier rather than later in their disease progression? The Mexicans operated on younger patients; the first Swedish attempts involved older patients. What percent of transplant patients actually improve and to what extent? Is the improvement sustained? Because of these uncertainties, let alone the cost of the operation (estimated to be about $80,000, including preoperative, surgical, and recuperative time in the hospital), many were asking in late 1987, "Are we ready for this procedure?"[6]

In early April 1988, at a meeting organized by the United Parkinson's Disease Foundation, the 15 American teams that had performed transplantation on approximately 100 patients during the previous 18 months convened in Chicago to compare their preliminary results.[7] In contrast to the Mexican patients, reported to have done astonishingly well, the results of the American transplants were profoundly disappointing, so much so that of the 10 medical centers where the procedures had been done, only two were still accepting patients for the operation.

While the neurological community waits and continues to assess the transplant patients for progress, the high-tech world of medicine moves forward. Because of the proven success of fetal tissue in transplantation, the assertion is that if the operation is to be effective at all, it must involve transplantation of immature and "plastic" fetal tissue rather than the patient's aging medullary tissue. Since there are an estimated 1.5 million elective abortions in the United States each year, there is an abundance of tissue available with great potential, advocates argue, in the treatment of not only Parkinson's disease but possibly diabetes, Alzheimer's disease, and other disorders. In January 1988, the Mexican team that spearheaded the adrenal procedure reported two such fetal transplants without any postoperative complications and with improvement in the disability rating scales over preoperative evaluation.[8] As of late September 1988, neurosurgeons in Cuba had performed another 10 transplants. Swedish physicians have performed the procedure for two women, both in their 50s, suffering from severe rigidity and tremor. The implant, a suspension of brain cells from four fetuses, was injected into three foci in the patients' brains: two in the putamen and one in the head of the caudate.[9] Using fetal tissue, however, even in the context of treating human disease, raises many serious ethical and legal questions and problems, not the least of which would be the viewing of an aborted fetus as a "marketable product and commercial prize."[10]

Notwithstanding these issues, it is predicted that researchers in many countries will soon begin treating patients by performing fetal brain transplants. To date, in this country, doctors have used fetal tissue only in experimental animals suffering from conditions mimicking the human ailment. However, in the closing weeks of 1988, using private funds to finance the cost, physicians at the University of Colorado and at Yale University transplanted fetal neural tissue into the brains of Parkinson's disease victims. Government funding for this fetal research had been terminated by the Reagan Administration during the week of April 17, 1988. The use of intentionally aborted fetal tissue by government scientists was banned until a panel of experts and ethicists could examine the ethical implications of the practice. Experiments involving tissue obtained from miscarriages, however, can proceed. The controversy is inflamed even more because the most useful fetal tissue, that which is most likely to "take," is from induced abortions.[11]

In December 1988, after months of discussion and debate, the blue ribbon panel said research on human fetal tissue transplantation should go forward and recommended the moratorium be halted (by a vote of 17 to 4).[12] The consensus opionion was offered by Judge Arlin Adams of Philadelphia who indicated that "the panel has carefully weighed concerns over abortion against concerns for medical research that could improve the lot of thousands of Americans and concluded that research must go forward as long as carefully crafted safeguards are in place."

In summary, as one author has recently observed,[7] the prospects for CNS transplantation as therapy for Parkinson's disease "are perhaps dimmer in the short term but certainly brighter in the long term."

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