COMMENTARY

Neural transplantation in Parkinson's disease: an update.

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It has been over 100 years since the first published account of neural transplantation in which Thompson reported grafting cat neocortex into the occipital cortex of dogs (1). Since Thompson's seminal publication of 1890, a great deal of animal research has been conducted in neural transplantation. However, it was not until the late 1970s that a number of laboratories around the world began working feverishly toward developing clinical trials in neural transplantation for Parkinson's Disease (PD).

Although laboratory results with fetal tissue grafting in the parkinsonian rodent model proved to be superior to that of adrenal medullary tissue, adrenal tissue was transplanted in humans first. This circumvented both the ethical and complex immunological issues that surrounded the use of fetal tissue.

The first human transplant for PD was conducted in Sweden in 1982 using adrenal medullary autografts transplanted into the striatum of a parkinsonian patient (2). The initial enthusiasm for the dopamine synthesizing adrenal medullary tissue stemmed largely from the impressive clinical improvements reported by Mexican neurosurgeon, Ignacio Madrazo (3). In the US alone, over 100 parkinsonian patients went on to receive adrenal medullary autografts (Bakay, 1989). However, by the end of the decade, most researchers had abandoned the largely disappointing adrenal medullary transplantation for the more promising fetal mesencephalic grafting.

Today, scientists believe that PD exerts its devastating effects by slowly destroying the dopaminergic cells of the substantia nigra causing denervation of the striatum. As the dopaminergic cells die beyond a critical number, PD sufferers begin to experience the hallmarks of the disease: increased rigidity, resting tremor and bradykinesia. While L-dopa has revolutionized the medical treatment of PD, many patients go on to become refractory to pharmacotherapy and may require surgical intervention. The goal of neural transplantation is to restore the dopaminergic content of the impoverished striatum and reconstitute the normal nigrostriatal pathway.

The year 1997 marks the tenth anniversary of the first human fetal mesencephalic transplant in humans (5, 6). Where does neural transplantation stand today? Is neural transplantation for PD any further ahead than it was 10 years ago? Is neural transplantation going to become a routine treatment for medically refractory Parkinson's Disease? What does the future hold for neural transplantation and PD?

The 1980's nurtured some pessimism regarding neural transplantation for PD, stemming largely from the failed adrenal medullary grafting trials as well as the ban on government funding of human clinical trials during the Reagan and Bush administrations in the United States (lifted by the Clinton administration in 1992). However, the 1990's seems to hold great promise for fetal mesencephalic grafting in the treatment of medically refractory PD.

If one compares the history of neural transplantation to cardiac transplantation, a similar picture emerges. The first published experimental heart transplant was performed by Carrel and Guthrie in 1905 at the University of Chicago (7). The first successful human to human heart transplant was performed by Dr. Christiaan Barnard in 1967. It was not

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until the late 1970's, however, that heart transplantation became a routine treatment for endstage heart disease, highlighting the period of development and refinement required of any revolutionary new treatment prior to becoming a routine procedure.

Neural transplantation, while approaching its clinical adolescence, continues to advance as it addresses issues surrounding embryonic donor age for maximal graft survival, transplantation technique (suspension vs. solid graft), use of neurotrophic factors, graft placement, graft regulation, immunosuppression and alternative cell sources.

An additional challenge facing neural transplantation in PD recently has been the re-emergence of the highly publicized pallidotomy and thalamotomy in which neurosurgeons stereotactically lesion different areas of the brain in an attempt to alleviate the symptoms of PD. While the popular media continues to herald these procedures as new revolutionary treatments for PD, these surgeries have been routinely performed for well over 40 years. The revival of these procedures can be largely attributed to the technical leaps made in both neuroimaging and intra-operative recordings, making these surgeries more accurate than ever before. Both procedures have enjoyed reasonable successes in the alleviation of parkinsonian symptoms. However, long term data is still lacking.

In contrast to these ablative procedures, which historically have been targeted at only one feature of PD (e.g. tremor or rigidity), it is thought that neural transplantation may actually have a broader effect on PD symptomatology. This is due to the fact that its aim is to reconstruct the nigrostriatal pathway.

Proceedings from 6th International Conference for Neural Transplantation in San Diego, California this past February proved very exciting . Much of the program focused on alternate cell sources, including genetically engineered cells that overexpress tyrosine hydroxylase, the rate limiting step in dopamine synthesis.

Genetically engineered cells will drastically change the face of neural grafting. These cells will provide a constant source of tissue for transplantation and avoid the difficulties surrounding procurement and storage of cells, as well as the ethical issues surrounding the use of fetal tissue.

In addition, an explosion of presentations were given regarding spinal cord injury, Huntington's disease and Alzheimer's disease, all of which are the challenge of tomorrow for neural transplantation.

Currently, two double-blind, randomized trials funded by the National Institute of Health (NIH) are well underway in the USA (University of Colorado, Denver and University of South Florida, Tampa). Several other groups are participating in their own clinical trials, including a Phase II trial at Dalhousie University, Halifax, Nova Scotia, the only neural transplantation program in Canada, headed by neurosurgeon, Dr. Ivar Mendez.

While preliminary results from the ongoing trials are promising, it will not be until the 1999 International Neural Transplantation meeting in Denmark that the future of neural transplantation for PD will be cast. At that time, the eagerly anticipated results of the randomized clinical trials will be unveiled to the world, firmly positioning Halifax as a world leader in the surgical treatment of PD.

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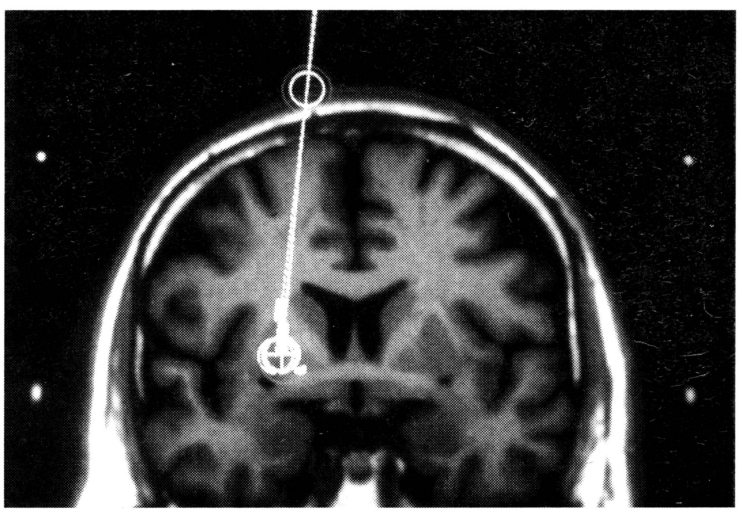

MRI surgical planning for neural transplantation in a parkinsonian patient, Halifax, NS.