More than 20 years have elapsed since the first failed trials of adrenal transplantation for Parkinson’s disease (PD). The reasons for the failure of adrenal and human and porcine fetal transplants to significantly improve motor disability in PD are complex and include difficulties translating from animal models to human disease, investigator bias, and placebo response. Now that restrictions on federal funding of embryonic stem cell research have been lifted, the lessons of this failed history may guide this new generation of investigators in cell-based PD therapy.

A Growing Interest

“One faces the future with one’s past.” —Pearl S. Buck

Scarcely a clinic day passes without a patient inquiring about the future of the stem cell cure for Parkinson’s disease (PD). Indeed, PD has long been thought to present ideal opportunities for restorative cell-based approaches. The motor syndrome of PD relates primarily to deficiency of a single neurochemical—dopamine, and the syndrome responds well to replacement of that chemical. Degenerating dopamine cells populate, and their terminals project to relatively small neuroanatomic regions (substantia nigra and striatum, respectively). It would seem relatively simple to implant cells of a single type into a small target area. Thus, cell transplantation seems feasible in this population. Indeed, cell transplantation seems feasible in this population. Indeed, well-entrenched toxin-based animal models of nigrostriatal degeneration have yielded a wealth of preliminary data supporting cell transplantation, and open-label studies using these approaches in small series of PD subjects have been universally encouraging. Yet, no such “brave new world” interventions have survived the rigor of the double-blind placebo-controlled study. This paper examines the history and possible reasons for these disappointments.

Cell transplantation in PD

The story of transplantation in PD began in April 1987, when Madrazo, et al. published a breathtaking report that two patients with advanced PD had responded dramatically to implantation of autologous adrenal medullary tissue to the non-dominant caudate nucleus. Surprisingly, the benefit was bilateral despite the unilateral procedure. Later that year, Lindvall, et al. reported somewhat disappointing results following transplantation of adrenal medullary tissue into the putamen in two PD patients. The Madrazo report unleashed a veritable frenzy, as many centers across the world began performing this procedure, using variable methods of patient selection, tissue dissection, preparation, and implantation and post-operative assessment. No prospective studies employed a sham surgery control, and it only gradually became apparent that clinical effects were less robust and long-lived than initially reported and side effects were significant, especially in older subjects. Clinical, imaging, and pathological studies showed poor survival and integration of adrenal medullary grafts, and the procedure was abandoned. One positive outcome of this failed line of research was the development of a systematic evaluation tool for PD surgeries, the Core Assessment Protocol for Intrastriatal Transplantation (CAPIT) in PD.

At the pre-clinical level, human fetal nigral tissue eclipsed adrenal medullary transplants. Investigators quickly translated these pre-clinical successes to a series of open trials of unilateral or bilateral implantation of human fetal substantia nigra tissue into the striatum. Preliminary results suggested substantial improvement (up to 55 percent) in the severity of motor impairment after overnight withdrawal of dopaminergic drugs. Parallel post-operative improvements in striatal 18F-fluorodopa uptake hinted at restoration of striatal dopamine innervation in some series.

A review of 70 well-documented published cases encompassing a number of methodological and evaluation tech-
niques suggested that most subjects had moderate clinical benefit from six to 24 months after transplant, but benefit did not increase between six and 24 months and levodopa requirements did not significantly decline over time.35

In the United States, fetal transplantation research initially took place in the absence of federal funding, consequent to an executive order in 1988 by then-President Ronald Reagan prohibiting funding this type of research. President Clinton reversed this ban in 1992, and the National Institutes of Health (NIH) specifically sought proposals for more rigorous study of fetal transplantation in PD.

Two randomized, double-blind, sham surgery-controlled studies funded by the NIH together enrolled 74 subjects. Freed, et al. randomly assigned 40 subjects with advanced PD to bilateral putamenal implantation of cultured fetal mesencephalon or to sham surgery. The study did not meet its primary outcome: change in a subjective rating scale. However, secondary analysis showed younger patients had significant improvements in objective motor ratings, and PET scan showed improvement in striatal 18F-fluorodopa uptake.36

Olanow and colleagues conducted a double-blind study that compared two doses of fetal tissue to a sham procedure in 34 subjects with severe PD. After two years, there was no significant improvement in motor disease severity in the transplanted group, though milder subjects did have a significant improvement, and PET scans improved.37 A few autopsy studies confirmed that grafted fetal nigral cells survive and reinnervate the putamen.38 That the transplants did have a biological effect was brought home by the observation that 12 to 57 percent of subjects developed peculiar involuntary movements in the legs three to 12 months after surgery. These movements most resembled the diphasic dyskinesias seen in a subgroup of PD patients in the “off” state.37 One very rare but sobering finding is the development of masses or cysts in a few parkinsonian subjects who have had fetal transplants.31,39,40 Recent studies have also suggested that grafted tissue may not be spared the degenerative process in PD. Loss of dopamine neurons and Lewy body formation in grafted cells have recently been reported in post-mortem studies of fetal transplant recipients.41

Ethical concerns about the procurement and use of human fetal tissue encouraged the development of other sources of tissue for transplantation. Following promising pre-clinical work, porcine fetal nigral cells were transplanted into one striatum in 12 PD subjects in an open-label trial. Measures of motor severity improved 19 percent on average in evaluable subjects. Improvement was bilateral.32-34 Following this, a double-blind study was undertaken in 18 subjects, randomized to be implanted with 48 million cells bilaterally with cyclosporine immunosuppression or to placebo surgery. Subjects in the active and placebo groups had similar improvement, and development of the treatment was stopped. No peer-reviewed publication ever appeared.

Pluripotent stem cells seem to be the next horizon for cell-based therapies of PD. An unending supply of these cells would obviate problems with obtaining ample fresh fetal tissue, presuming they could be prodded to irreversibly differentiate into dopaminergic neurons suitable for transplantation. In the US, however, most embryonic stem cell scientists have not had access to federal funding since August 9, 2001, when then-President George W. Bush prohibited NIH funding for research using stem cell lines created after that date. On March 9 of this year, President Barack Obama signed an executive order allowing NIH funding for research on newly established embryonic stem cell lines. Now we may be poised on the threshold of human clinical trials of stem cell transplants in PD.

**Thoughts for the Future**

Before embarking on this course, however, we would do well to reflect on the lessons of history in cellular transplantation in PD. These are:

1.) Results from open-label trials are poorly predictive of the results of sham-controlled trials. Bilateral improvements and large effect sizes may reflect investigator bias and the placebo effect, formidable opponents in the design of controlled studies.

2.) The relationship between cell survival and production...
of dopamine and clinical benefit appears complex. Grafts that survive and show integration with the host do not necessarily produce robust clinical effects. Neuroimaging makes for nice pictures but may not be a useful outcome if it doesn’t agree with clinical outcome.

3.) Sometimes, the most prominent biological effect is a side effect.

Finally, new evidence illustrates the extent of non-nigral pathology in PD. Indeed, the nigral degenerative changes are side effect.


