

**What's Hot Column--January 2009**  
**Why are Transplant Trials Struggling to Succeed in the Treatment of**  
**Parkinson's Disease?**

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Recently, another transplant trial in Parkinson's disease was reported as a failure (Spheramine). It seemed rational many years ago when scientists proposed cell replacement as the penultimate neurorestorative therapy for Parkinson's disease, but sometimes rational is not enough. The track record has been less than expected. There have however, been many lessons learned and the experience will hopefully help us toward better therapies in the future.

Several preliminary open-label pilot studies of various transplant techniques for human Parkinson's disease were observed to have varying degrees of success. Transplants with adrenal medullary cells and then human embryonic dopaminergic cells were sought as a potential treatment for advanced Parkinson's disease. Two independent double-blind studies (investigator blind and examiner blind) failed to reveal adequate efficacy when compared to a sham group (a group who received burr holes in the head but no transplant), although the younger patients seemed to display some positive motor benefits. The most recent exclamation point on transplant therapy occurred when Spheramine was reported as a failure. Spheramine was a cell based therapy for transplantation into Parkinson's disease brains in a double-blind trial (half got spheramine and half got sham surgery). Spheramine consisted of human retinal epithelial cells attached to what was called a microcarrier support matrix which was designed to help survival. One of the rationales for the study was the finding that inner retinal cells could produce dopamine. Recent positive unblinded studies of Spheramine led to the blinded trial which did not meet its primary outcome (15).

There are many potential reasons for the failure of the transplant trial experiences. Perhaps the most compelling reason for failure is the complex nature of the multiple motor and non-motor circuits affected(1-5) in Parkinson's disease. The transplants only attempted to replace dopaminergic cells in one degenerated area of the brain (the putamen). Future approaches may need to broaden their scope to account for the many brain systems involved in the pathogenesis of Parkinson's disease. Of particular interest is that Parkinson's disease is now known to be motor as well as non-motor (depression, anxiety, sexual dysfunction, etc.), and these non-motor systems deserve particular attention.

The use of sham surgery, or drilling burr holes in the skull but not implanting cells, in half the patients in the transplant trials has drawn much ethical discussion. It is interesting that the open-label unblinded effects of the pilot surgery that led to the larger blinded trials were positive, but when a sham group

was utilized the placebo effects cancelled out many of the potential benefits. Additionally, the group that received the transplanted cells also developed unacceptable side effects (e.g. dyskinesias), as compared to those in the sham group. Finally, if the study was positive and safe, the sham group would have ultimately been offered the transplanted cells(6-16). Sham surgery therefore proved a reasonable and important approach.

Patients enrolled in both of the large double blind placebo-controlled trials for transplantation of embryonic dopaminergic cells developed a unique and never before observed side effect referred to as runaway dyskinesia. The term runaway dyskinesia has been coined because the extra movements (or dyskinesias) occurred in both the “off” medication state as well as in the “on” medication state. Normally, dyskinesias in patients without transplants only occurs in the “on” medication state. It is still speculative as to why this side effect occurred in the transplanted patients, but most experts believe that in some way the grafted tissue reconstituted the circuitry in an aberrant way(9, 17, 18).

The most interesting findings derived from the transplant studies are the imaging data and the post-mortem data which have revealed that the transplanted cells survived and prospered in their new home. This finding is encouraging for the future of the transplant field, however, it reminds us that the gold standard for improvement is not the MRI scan, but rather the patient(18, 19). Multiple groups have reported the phenomenon of spreading neurodegeneration from the host tissue into the newly grafted cells. Careful examination of post-mortem brains following embryonic fetal cell transplants has shown evidence of the Lewy Body and other neurodegenerative features in the previously unaffected cells transplanted into the host. Scientists are hopeful that the explanation of this phenomenon will help unlock some of the mysteries surrounding Parkinson’s disease(19, 20).

As the Parkinson’s disease transplant field moves forward, into new areas such as stem cells and gene therapy, it is important that the lessons learned from the failed transplant trials are incorporated into new strategies for success. It should be pointed out that hope should remain strong as we have accomplished the proof of principle in making cells survive and prosper after transplant—now we need to focus on improving their functionality and reconstituting a complex broken circuitry.

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