Commentary - The Case for Deep Brain Stimulation

Arguably, DBS is the most effective treatment for many movement disorders. It succeeds in cases when all manner of pharmacological and biological (fetal cell transplants) treatments have not. For example, in clinical trials of Parkinson's disease, all reasonable pharmacotherapies have to be unsuccessful before patients can receive DBS (Deep-Brain Stimulation for Parkinson's Disease Study Group 2001), and, despite previous treatment failures, the large majority of patients improve substantially. In other clinical trials, where patients with Parkinson's disease were randomly assigned to medical therapy or to DBS, DBS produced greater clinical benefit (Schupbach, Maltete et al. 2007; Weaver, Follett et al. 2009). In clinical trials of fetal cell transplants, patients regressed to baseline disability within 12 months (Olanow, Goetz et al. 2003), whereas those receiving DBS experienced sustained benefit for 5 or more years (Pahwa, Lyons et al. 2006; Krack, Batir et al. 2003). Indeed, the majority of patients who received fetal cell transplants experienced "runaway" dyskinesias that were controlled in many cases with DBS (Olanow, Goetz et al. 2003; Graff-Radford, Foote et al. 2006). To date, no one has argued convincingly that stem-cell implantation will be any better than fetal-dopamine-cell transplantation. Although gene therapy is still early in its development, studies of transfecting glutamic acid decarboxylase (GAD) into the subthalamic nucleus (STN) report benefits on the order of 30% (as measured on the Unified Parkinson's Disease Rating Scale) (Kaplitt, Feigin et al. 2007). In contrast, DBS provides sustained improvement on the order of 50% or higher. The benefits of intra-parenchymal injections of nerve growth factors in patients with Parkinson's disease have been no better than those with placebo. The potential risks of stem cells transplants,

viral vector-mediated gene therapies, and intra-parenchymal injections of biological agents are not likely to be any less than those of DBS. All require surgical invasion of the brain.

Similarly, DBS is successful in other conditions where pharmacotherapy has failed, such as essential tremor (Koller, Pahwa et al. 1997), tremor secondary to other causes (such as multiple sclerosis) (Montgomery 2008), obsessive-compulsive disorder (Abelson, Curtis et al. 2005), the hyperkinetic symptoms of Tourette's syndrome (Shahed, Poysky et al. 2007), and more.

Despite its clinical superiority and relatively modest risks, DBS has not captured the imagination of neurologists, geriatricians, generalist physicians, or the public at large, as has stem cell transplantation or gene therapy. This lack of attention is important and intriguing, and it has implications for the nature of scientific progress in general. Perhaps pharmacological, stem cell, and gene therapies provide the comfort of familiarity. Perhaps these therapies are seen as natural extensions of current theories of disease pathoetiology and pathophysiology. If so, it is a false comfort, because many of the current theories of physiology and pathophysiology are fatally flawed (Montgomery 2007) and continued adherence to them will only delay new knowledge and better treatments. Perhaps it is because medical schools now teach less physiology - particularly systems physiology - and relatively more molecular biology and pharmacology. Even most current theories of basal ganglia physiology and pathophysiology are not physiological in nature. Rather, they are inferences from anatomy and pharmacology: they are based on the paradigms of *anatomy as physiology* and *pharmacology as physiology* (Montgomery 2007). Abraham Maslow's adage, "When the only tool you have is a hammer, everything looks like a nail," is relevant here; many neurological disorders are still thought to be

neurotransmitter disorders, and Parkinson's disease is thought to result from dopamine deficiency.

Deep brain stimulation has a great deal to teach us, if we will but listen. Already, it is clear that the mechanisms of DBS are not analogous to those of pharmacotherapy. DBS is telling us something radically new and different.

References:

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