The Continuing Saga of GDNF and Parkinson Disease

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Parkinson, Parkinson's

Glial cell line-derived neurotrophic factor (GDNF) for the treatment of Parkinson disease continues its roller-coaster trajectory (see Parkinson Disease: The Ups and Downs of Developing Therapies, Applied Neurology, April 2005, page 11). Evidence of dopamine production and nerve fiber sprouting in the brain of a deceased clinical trial participant1 came hot on the heels of a legal setback for 2 other trial participants who are suing Amgen Inc in an effort to continue receiving the controversial treatment.

In April, Richard Suthers of Greenlawn, NY, and Niwana Martin of Harpers Ferry, WV, filed suit, seeking a preliminary injunction to obtain GDNF from Amgen while legal proceedings continue. But on June 6, a judge in a US district court in Manhattan ruled against the patients, writing that their relationship was with New York University, which ran the clinical trial, and not the company.

Just 1 month after the judge's preliminary ruling, the autopsy report was released of a 62-year-old man treated for 43 months with continuous direct-brain infusions of GDNF. The man had died of a heart attack 3 months after Amgen halted clinical trials in September 2004 in response to lack of effect in treated monkeys. The man had been 1 of 5 patients in an open-label trial begun in 2001 by Steven S. Gill, FRCS, and colleagues at the University of Bristol Institute of Clinical Neuroscience at Frenchay Hospital in the United Kingdom. This trial2 was the inspiration for the larger trial in which Suthers and Martin had participated. All of the initial 5 patients improved. Seth Love, MBBCh, PhD, a neuropathologist at Frenchay Hospital, led a team that analyzed the brain of the patient who died of a heart attack. Because the man had left hemiparkinsonism, GDNF had been delivered to his right posterodorsal putamen. He therefore served as his own control. At and until 24 months, the Unified Parkinson's Disease Rating Scale showed a 38% improvement during the "off" medication period for both sides, as well as an 18% increase in uptake of 18F-dopa in the entire putamen and 91% in the posterior one third of the putamen. In the uninfused side, a 7.4% decrease in uptake in the entire putamen was seen, and related motor scores declined after 24 months.

Autopsy revealed the catheter track, with some clustering of astrocytes but inflammation only at the tip, amid histologic hallmarks of Parkinson disease. Labeled antibodies to tyrosine hydroxylase, the rate-limiting enzyme in the dopamine biosynthetic pathway, were 5-fold more concentrated in the right posterior putamen than in the corresponding, nontreated region on the left. Strong expression of growth-associated protein 43 on the right side of the posterior putamen suggested nerve fiber sprouting in the substantia nigra.

"This report is of great interest to neurologists and scientists who work in this field because it does demonstrate that GDNF is having an effect on the dopamine system in the brain of a patient with Parkinson disease. But as the authors point out, it is unclear what the finding actually means in terms of whether or not GDNF promotes neuronal growth in humans," said William J. Weiner, MD, director of the Maryland Parkinson's Disease and Movement Disorders Center at the University of Maryland School of Medicine in Baltimore, referring to Love and his team, which includes Gill. A sense of déjà vu lurks in the background, recalling the fetal transplant work of the late 1990s that also showed sprouting but "did not translate into benefit for Parkinson patients," Weiner added.

Love and colleagues worded their conclusions guardedly. Although they call this work the first evidence of sprouting of dopaminergic fibers, they offer 2 hypotheses to explain the tyrosine hydroxylase distribution: either the sought-after resprouting, or up-regulation to compensate for malfunctioning nerve fibers. The man's progress was similar to that of the other 4 participants in the open-label trial.2

REFERENCES
1. Love S, Plaha P, Patel NK, et al. Glial cell line-derived neurotrophic factor induces neuronal

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[1] [http://www.psychiatrictimes.com/authors/ricki-lewis-phd](http://www.psychiatrictimes.com/authors/ricki-lewis-phd)