NEUROSCIENCE

Researchers Broaden the Attack on Parkinson's Disease

Because there is no cure for Parkinson's disease and no therapy that is effective in the long term, researchers are urgently seeking better treatments. Among the treatments now being investigated, the most controversial seeks to replace the brain neurons that die in Parkinson's disease with transplants of fetal tissue. The treatment shows promise, but it is fraught with political and ethical problems because of its dependence on the use of aborted human fetuses.

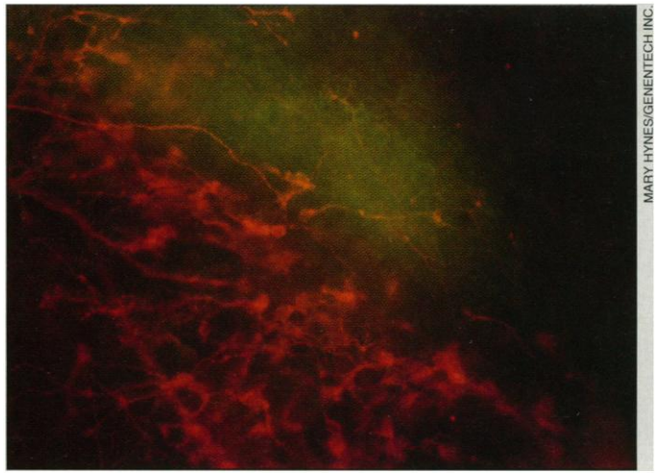
But four papers published this month suggest that the search for new treatments is broadening out. Two of the papers suggest ways to improve the neuron transplants or make them independent of the availability of fresh fetuses; the other two take an entirely different tack, suggesting that it might be possible to prevent the neurons at risk in Parkinson's from dying by injecting a growth factor into patients' brains. "It is difficult at this point to guess which [of these therapeutic strategies] will eventually turn out to be the most efficient," says neural graft pioneer Anders Björklund of the University of Lund, Sweden. "But one should expect that there will be very interesting developments along these lines in the next few years."

Researchers have been highly motivated to find such new strategies because, despite the large amount of effort put into neuronal transplants during the past 8 years, the therapy has suffered from two major handicaps. Because of the ethical controversy, federal funding of the research was prohibited from 1988 until 1992, when President Clinton lifted the ban. During that period, the research that was done (in other countries or with private funding) gave variable results, with some patients showing tantalizing improvement while others continued to decline.

Many researchers think low survival of the transplanted tissue accounts for at least some of the variability. "Right now what we do is put in as much tissue as possible, and hope and pray that enough cells survive," says University of Chicago transplant researcher John Sladek. The result is that investigators use brain tissue from four to 10 fetuses for each graft.

Better graft survival might reduce the need for so many fetuses, and in a step toward that end, a research team at the University of California (UC), San Diego, led by neuroscientist Fred Gage, recently demonstrated a means of boosting the survival of neurons transplanted into the brains of rats. The group mixed the neurons to be transplanted with nonneuronal cells engineered to produce basic fibroblast growth factor (bFGF), a protein that nurtures many types of neuronal cells in tissue culture. They performed their experiment in rats that had been given a Parkinson's-like condition by injecting 6-hydroxydopamine, a neurotoxin that specifically kills the same set of dopamine-producing neurons that die in Parkinson's disease, into their brains.

When the researchers transplanted the engineered fibroblasts along with fetal dopamine-producing neurons (known as dopaminergic neurons) into the animals' brains, they saw a marked improvement in the survival of the transplanted neurons. Ten times as many transplanted neurons survived in the animals that received the bFGF-producing cells as survived in control animals.



MARY HYNES/GENENTECH INC.

Transplant source? Dopamine-producing neurons *(red)* are induced in embryonic midbrain tissue by coculture with floor-plate cells *(green)*.

What's more, Gage says, the Parkinsonian symptoms were completely reversed in the treatment group, while those of the control rats remained essentially unchanged. Those results, published in the January issue of *Nature Medicine*, represent "the most substantial improvements in cell survival" yet, says Björklund.

It's still too early to tell whether bFGF will end up in clinical use, but researchers are optimistic that it or one of the other growth factors that they plan to test will help sustain the fetal transplants. The growth factors "should have clinical relevance, in the near term, in terms of getting better [graft] survival," says Curt Freed, director of the neurotransplant program for Parkinson's disease at the University of Colorado Medical Center.

Even better, says Björklund, would be finding a way of obtaining dopaminergic neurons that is "largely independent of a continuous supply of fetal material." And that's where the second paper, from a group led by Arnon Rosenthal at Genentech, comes in. Rosenthal and his colleague Mary Hynes were searching for the signals that normally trigger differentiation of dopaminergic neurons during development. They teamed up with Marc Tessier-Lavigne of UC San Francisco, who studies a part of the developing nervous system called the floor plate. "We realized these [dopaminergic] neurons were born near the [floor plate]," says Hynes, and so they wondered whether something in the floor plate might trigger their differentiation.

Their hunch proved correct. In the 13 January issue of *Cell*, they report that floor-plate cells from embryonic rats can induce undifferentiated neuronal precursor cells taken from the rats' midbrain region to become dopaminergic neurons, in both living embryos and the test tube. Even precursor cells that would normally go on to a different fate could be coaxed into becoming dopaminergic neurons instead.

This finding suggests that researchers may be able to grow dopaminergic neurons from undifferentiated precursors in the test tube—which would reduce or even eliminate dependence on fetuses. Working toward that end, Rosenthal says the team is trying to identify the chemical signal in the floor-plate cells that triggers differentiation and is also trying to find a way to grow the precursor cells in continuous culture so they won't have to be freshly collected from fetuses, as they were for the current experiments. The Genentech approach "has the potential to produce almost pure dopaminergic neuroblasts [the nerve cells' precursors] for grafting," says Chicago's Sladek.

Those are encouraging developments in grafting. But many of those gazing into the future of Parkinson's therapy see a time when there will be therapies that rescue a patient's own dopaminergic neurons, making neuron grafts unnecessary. One candidate as a substance for preventing the death of dopaminergic neurons is glial-derived neurotrophic factor (GDNF), a protein isolated in 1993 by Frank Collins and his colleagues at Synergen Inc., a biotechnology company in Boulder, Colorado. In work reported in two papers in this week's issue of *Nature*, Lars Olson of the

Karolinska Institute in Stockholm, Barry Hoffer of the University of Colorado and their colleagues, and Franz Hefti and Klaus Beck of Genentech and their co-workers show that direct injections of GDNF into the brains of rats and mice can save dopaminergic neurons that have been damaged by either the neurotoxin MPTP or surgical injury.

In the Genentech group's experiments on surgically injured rats, the control animals lost 50% of their dopaminergic neurons, while animals that were treated with GDNF after the injury retained nearly normal numbers of healthy cells. Hoffer's group had similar results with mice treated with MPTP, and in addition found that the GDNF injections also alleviated the Parkinson's-like symptoms induced by MPTP. (The neuron-severing injury used by Hefti's group doesn't produce symptoms in the rats, so they couldn't test for recovery.)

Although preliminary, these experiments have raised hopes that GDNF will have similar neuron-saving effects in humans. But Freed cautions that it's not yet clear whether the results can be extrapolated to humans, because the existing animal models are only approximations of Parkinson's. "We simply don't know," he says, what effects growth factors such as GDNF might have in human patients.

We might know soon, though. Amgen Pharmaceuticals bought Synergen last month and plans to move toward clinical trials, although Collins, now at Amgen, says there is no schedule yet for the trials. The first trials will probably involve pumping GDNF directly into the patients' brains, because it is a protein that does not cross the blood-brain barrier. If GDNF proves successful, Amgen and other companies will no doubt search for a small molecule that mimics the protein's effects but can cross the blood-brain barrier and therefore can be administered systemically.

Will this therapeutic approach eventually make brain-cell grafts obsolete? "It is too early to call it," says Hefti, because the approaches to both transplantation and rescuing the patients' own neurons are in such early experimental stages. "Both approaches are very valuable at this point," he says, "and they should be pursued." And it's possible that one of them will prove to be a much better substitute for the existing therapies and their merely temporary respite from the devastation of the disease.

–Marcia Barinaga

Additional Reading

L. J. Fisher and F.H. Gage, "Intracerebral transplantation: Basic and clinical applications to the neostriatum," *FASEB Journal* **8**, 489 (1994).

L.-F. H. Lin *et al.*, "GDNF: A glial cell line–derived neurotrophic factor for midbrain dopaminic neurons," *Science* **260**, 1130 (1993).

Quasars and a Dwarf Star Break the Rules in Tucson

Earlier this month, more than 2000 astronomers convened in Tucson, Arizona, for the American Astronomical Society's largest meeting ever. Even the war drums beaten by a few local Apaches and their supporters, protesting a University of Arizona telescope project, could not drown out lecture-hall and corridor discussions of topics such as naked quasars, flaring stars, and planetary searches.

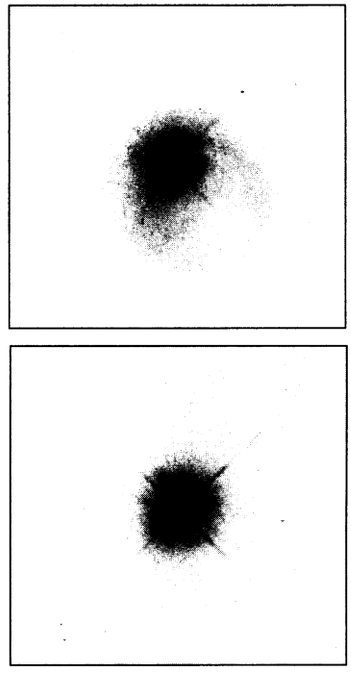
Quasars Bare All

At a press briefing at Tucson, John Bahcall of the Institute for Advanced Study (IAS) in Princeton, New Jersey, noted that colleagues jokingly attribute his success as an astronomer to a series of spectacular failures. Bahcall, for instance, is a leading authority on the "solar neutrino problem"—researchers' failure to find a good half of the neutrinos that theory predicts should be streaming from the sun. And just a few months ago, Bahcall led a team that failed to find as many dim red stars as some theorists had predicted, apparently eliminating the most conventional explanation for the mysterious dark matter that is thought to permeate our galaxy's outer regions.

Now Bahcall seems to have scored another dramatic observational "failure." Taking the closest look ever at the mysterious, powerful beacons known as quasars with the repaired Hubble Space Telescope (HST), he and his colleagues were largely unable to find the galaxies that are thought to fuel them. "We've taken a giant step backward. We need to rethink how quasars shine," argues Bahcall. Not all astronomers are going that far, but nearly everyone is at a loss to explain Bahcall's "naked" quasars. "This was completely unexpected. It's the most surprising finding to come out of HST," comments Jeremiah Ostriker of Princeton University.

The desire to get a better look at quasars was one of the original motivations for the orbiting telescope. The standard view holds that quasars are supermassive black holes lurking at the centers of well-developed galaxies, where they generate their brilliant radiation by dragging in gas and stars. But spotting host galaxies within the quasars' glare was largely beyond the abilities of ground-based telescopes, which must peer through Earth's atmosphere.

The flaw in HST's mirror delayed the search for these galaxies, but after the optics were corrected in late 1993, most astronomers thought the telescope would quickly resolve the galaxies and support the standard view of quasars. But last February, when Bahcall, IAS colleague Sofia Kirhakos, and Donald Schneider of Pennsylvania State University began taking images of nearby, bright quasars, confusion set in. After processing each image by computer to subtract the light of the quasar, the astronomers were stunned to find that the first eight quasars were naked—"unclothed" as Bahcall modestly puts it. "We couldn't figure out what we were doing wrong," says Bahcall. "According to the paradigm, we expected the monster to be feeding on its environment. And we expected that environment to be visible." A measure of relief was finally provided by the ninth HST image, which showed an obvious host galaxy. But of the 15 quasars imaged so far, only four are clearly centered in host galaxies.



JOHN BAHCALL/INSTITUTE FOR ADVANCED STUDY/NASA

Naked came the quasars. Instead of the expected bright host galaxies, new Hubble images reveal only a hint of a host galaxy around one quasar (*above*) and the wispy remnants of a disrupted galaxy near another (*top*).

Some astronomers believe the standard picture of quasars may weather this latest spectacular Bahcall failure. "It's hard for me to believe that the galaxies are not there at some level," says Robert Williams, a quasar investigator and director of the Space Telescope Science Institute in Baltimore. Williams suggests that longer exposures or more sophisticated subtraction of the quasar light may be needed to see the hosts.