that the cells will engraft in the brains of experimental animals and is now testing them in models that mimic human diseases and spinal cord injury in preparation for a potential clinical trial next year. Snyder worries, however, that the field is becoming so hot that its credibility could be damaged by hype, and he says he aims to help deflate exaggerated claims.

Another small private company, NeuralSTEM Biopharmaceuticals of Bethesda, Maryland, plans to exploit human neural stem cells derived from embryos. Karl Johe, a former researcher in McKay's lab at NIH and now at NeuralSTEM, discovered a method of isolating and growing these cells in animals. NIH released the patent on the cells to NeuralSTEM, which was founded by McKay, attorney Richard Garr, and another investor. Garr, the CEO, says the company's first goals are to produce cells that can be transplanted into Parkinson's disease patients and develop vectors that can deliver therapeutic proteins to the brain.

A similar project is taking shape on the West Coast, under the direction of Nobuko Uchida, who previously worked in immunologist Irving Weissman's lab at Stanford University. Uchida is now chief of neurology research at StemCells Inc., which Weissman helped found. StemCells is a subsidiary of a public company known as CytoTherapeutics Inc., in Sunnyvale, California, which announced last year that it was shedding all other investments to focus entirely on stem cells. It aims to commercialize Uchida's pending patent on a method that uses surface markers to isolate adult neural stem cells from brain tissue. Once the cells are in hand, the goal is to use them to treat patients with neurodegenerative diseases.

Another company that aims to attack the same medical problems is Neuronyx Inc., which just set up shop this month in Malvern, Pennsylvania, with backing from Hubert Schoemaker, the former CEO of Centocor. Johnson & Johnson recently bought Centocor for $4.9 billion, and Schoemaker is using some of the proceeds to create his new company, which hopes to exploit embryonic stem cells for an agenda to be developed by research chief Tony Ho, a neuroscientist recently hired from Johns Hopkins.

Although most of this new business activity is taking place in the United States, several companies have sprung up elsewhere. ReNeuron, a small British company with a staff of about 17, is trying to commercialize stem cell work by three faculty members at the Institute of Psychiatry in London. With backing from the large biotech fund called Merlin Ventures, ReNeuron has established a line of neuroepithelial stem cells derived from fetal tissue. According to CEO Martin Edwards, the company hopes to begin transplanting these cells into stroke patients in a clinical trial "around the end of 2000." Stem Cell Sciences, based in Melbourne, Australia, which has ties to embryologist Austin Smith of the University of Edinburgh in Scotland, is raising money for unspecified therapies using stem cells.

It is of course far too early to judge the likelihood of success for any of these investments. But one thing is certain: We will be hearing a lot more about the promise of stem cells in the next few years.

–ELIOT MARSHALL

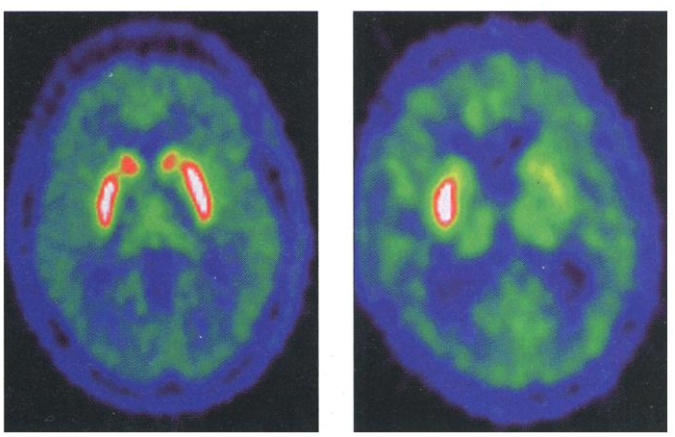
NEWS

Fetal Neuron Grafts Pave the Way for Stem Cell Therapies

A decade of experimental treatments using fetal neurons to replace brain cells that die in Parkinson's disease can provide lessons for planning stem cell therapies

Swedish neuroscientist Anders Björklund and his colleagues may have caught a glimpse of what the future holds for the treatment of failing organs. For more than 10 years, Björklund has been part of a team at Lund University in Sweden that has been grafting neurons from aborted fetuses into the brains of patients with Parkinson's disease. In many cases, the transplanted cells have dramatically relieved the patients' symptoms, which include slowness of movement and rigidity. That is just the kind of therapy that stem cell researchers hope to make routine for treating all sorts of degenerative diseases, if they can coax the cells to develop into limitless supplies of specific cell types that can be used to repair or replace damaged organs.

Although the current Parkinson's treatment uses fetal cells that have already developed into a particular type of neuron, the promising results represent a "proof of principle that cell replacement actually works," says Björklund. The results have given researchers increased confidence that, if they can manipulate stem cells to develop into the kind of neuron the Lund group and others are using—a big challenge—the new cells would take over the work of damaged cells in the brains of Parkinson's patients. If so, Parkinson's treatment could be among the first applications of stem cell therapy.



CREDIT: P. PICCINI *ET AL.*, *NATURE NEUROSCIENCE* 2, 1137 (1999)

Persistence. As shown by the red and white colored area, a fetal graft implanted in the brain of a Parkinson's patient 10 years ago *(right)* still produces normal levels of dopamine. A normal brain scan is at left.

The successes have also increased the urgency of developing stem cell treatments, because despite their promise, there are many reasons that fetal cells will never be widely used to treat Parkinson's disease. The reasons range from ethical concerns, such as the protests by antiabortionists that led the governor of Nebraska to urge that research involving fetal tissue be shut down at the University of Nebraska (*Science*, 14 January, p. 202), to the fact that there will never be enough fetal tissue to treat all the people who need it. Parkinson's disease afflicts 1 million people in the United States alone.

Researchers are now looking closely at the results from fetal cell transplants for lessons that will help guide future work with stem cells. There are still many hurdles to overcome, but this first round of cell replacement in the brain sets a "gold standard" that stem cells must meet if they are to become the basis for new Parkinson's treatments, says neuroscientist and stem cell researcher Evan Snyder of Harvard Medical School in Boston.

Parkinson's disease is a logical candidate for cell replacement therapy, in part because conventional treatments have had limited success. The disease is caused by the death, for unknown reasons, of a particular group of brain

neurons that produce dopamine, one of the chemicals that transmit signals between nerve cells. Afflicted people lose the ability to control their movements, ultimately becoming rigid. Treatment with levodopa (L-dopa), a drug that is converted to dopamine by the brain, alleviates these symptoms, but as the neurons continue to die, L-dopa's effectiveness wanes. Researchers first tried replacing the dopamine-producing cells by grafting into the affected region cells from the adrenal medulla gland. These cells are not neurons, but they make dopamine and can be coaxed to become neuronlike. The treatment reversed Parkinson's symptoms in rats, but produced little lasting improvement in human patients, probably because the cells died or stopped making dopamine, says John Sladek, chair of neuroscience at the Chicago Medical School.

Researchers have had better luck grafting immature neurons taken from aborted human fetuses. Dozens of patients who have received these experimental dopamine-neuron grafts over the past 10 years have had up to a 50% reduction in their symptoms. And the effects appear to last. Using positron emission tomography to image the brain, Olle Lindvall of Lund University and a team of colleagues in Lund and at Hammersmith Hospital in London reported in the December issue of *Nature Neuroscience* that, in one patient, the transplanted neurons are still alive and making dopamine 10 years after the surgery. That's encouraging, says neurotransplant researcher Ole Isacson of Harvard Medical School: Whatever killed the brain's own dopamine-producing neurons doesn't seem to have killed the transplanted cells.

Still, fetal cell transplants are plagued by problems that can never be overcome. Aside from ethical concerns about scavenging neurons from aborted fetuses, there are practical issues. It takes six fetuses to provide enough material to treat one Parkinson's patient, in part because as many as 90% to 95% of the neurons die shortly after they are grafted. Indeed, Lund's Björklund says, the cell supply is so limited that researchers have not even been able to test some possible avenues for fetal cell transplants. The neurons that die in Parkinson's originate in a brain region called the substantia nigra and send their long axons to several other areas, where they release dopamine. So far, researchers have put the cell grafts into only one of these areas, the putamen—and even there, they have not yet transplanted enough neurons to restore normal dopamine levels in most cases.

Even if researchers can develop techniques that diminish the fetal cell die-off, there will never be enough fetuses available to make this an "everyday procedure," says Sladek. What's more, the brain material recovered from aborted fetuses "comes out in a form that makes it difficult to ... standardize" in terms of quality and purity, Björklund says. This is likely why some patients do far better than others—uncertainty that would be unacceptable in a standard medical treatment.

> **"The ability to grow the cells of interest [from stem cells] will make this a routine technology."**
>
> —Ron McKay

Consequently, researchers are pinning their hopes on cultured stem cells. They would eliminate a continuing dependence on aborted fetuses, although the ethical concerns won't be completely laid to rest unless researchers can use stem cells obtained from adults rather than embryos (see p. 1418). And the supply of cultured cells could be unlimited, allowing tests of grafts into the putamen and possibly into other brain areas as well. The cell treatment, moreover, could be standardized and controlled to assure a more predictable outcome. "The ability to grow the cells of interest will make this a routine technology," predicts neuroscientist Ron McKay, whose team is working on ways to culture neural stem cells at the National Institute of Neurological Disorders and Stroke.

But to make this brave new world of cell replacement technology a reality, researchers must first learn how to keep stem cells dividing for many generations in culture and then be able to trigger them to differentiate into the type of neuron they want. Stem cells presumably have the ability to differentiate into any of the several different types of dopamine neurons the brain contains, but it may be crucial to use the specific type of dopamine neurons that die in Parkinson's. Researchers doing the fetal cell transplants specifically select these neurons—known as nigral neurons because they originate in the substantia nigra—when they harvest neurons for grafting from fetal brains. Nigral neurons are "genetically programmed and designed to be a dopamine neuron in the appropriate brain circuit," Sladek says.

Among other things, nigral neurons may respond better to local conditions, producing just enough dopamine. Experience with L-dopa treatment has shown that too much of the neurotransmitter can be just as problematic as too little, causing uncontrollable, jerky movements in patients. Researchers worry that stem cells coaxed to develop into dopamine neurons may become one of the nonnigral types and will not regulate their dopamine output in the appropriate ways. "It is like putting the right alternator into your car," Sladek says. "If you put in one designed for another model of car, it may not work as well."

Getting stem cells to differentiate into the right type of neuron may be only part of the problem. Neurons in their natural environment are surrounded by support cells called glia, which nurture the neurons and even modulate their activity, and optimal cell transplants may require replacing not only dopamine neurons but also the glia that normally surround them, Harvard's Snyder suggests.

But some researchers believe that the brain itself may be able to overcome the hurdles of producing both the proper neurons and the support cells they need. Snyder's lab has shown in animal experiments that stem cells put into the brain can be influenced by the brain environment to differentiate into both neurons and support cells. He envisions someday putting stem cells into Parkinson's brains and letting the brain tell them which cell types to become.

Even if it turns out not to be quite that simple, Parkinson's poses a much less daunting challenge for cell replacement therapy than do other neurological disorders. "The dopaminergic system is a fairly easy system to work with compared to sensorimotor or visual systems or spinal cord," says Isacson. That, he says, is because the nigral neurons lost in Parkinson's disease have a diffuse and relatively nonspecific network of connections in the brain areas they link up to, rather than the very intricate and precise connections made by neurons in many other parts of the nervous system.

The treatment of most other brain disorders would likely require coaxing new neurons to make very precise connections, a task that no one is sure how to achieve. But in the case of Parkinson's disease, simply getting neurons to release dopamine in the correct general area helps patients. Because of that difference, Isacson predicts that "it will take some time to get other diseases to benefit from all these discoveries." Nevertheless, a successful Parkinson's treatment based on stem cells would still be a dramatic achievement. "You would help a huge number of patients," he says, "as many as the surgeons could do."

–MARCIA BARINAGA