Brain-Grafting Work Shows Promise

Grafts can correct changes that occur in the brains of aged rats and may eventually be used to treat Alzheimer's disease

It is becoming increasingly likely, according to Anders Bjorklund of the University of Lund, that one day brain grafts will be used to correct Alzheimer's disease, a devastating and irreversible form of senility. At present, brain grafts are being tested in Sweden as a treatment for severe Parkinson's disease. Grafts also have been shown to correct some age-related changes in rats' brains, and, in experimental studies on rats, grafts have corrected biochemical changes in the brain that resemble those in Alzheimer's patients. However, a number of problems remain to be solved before extensive experimentation can be carried out in humans, not the least of which is where to obtain the brain tissue that will be grafted.

Bjorklund spoke about his group's recent work with brain grafts on 1 September at the Veterans Administration (VA) in Washington, D.C., at a meeting sponsored by the VA and the University of Michigan. He has been grafting brain tissue for a decade and is focusing, he says, "on those types of neuronal deficits that are related to the aging brain." These include a lack of brain acetylcholine, a neurotransmitter that is lost in Alzheimer's disease, and a lack of the neurotransmitter dopamine, which occurs to some extent in normal aging and to a far greater extent in Parkinson's disease.

Researchers believe brain-grafting may be successful in part because the blood-brain barrier keeps immune cells out of the brain, thus making the brain an immunologically privileged site. Of all the sites in the body, the brain may be the least likely to reject a graft of foreign tissue. Investigators have grafted brain tissues in rats that produce the neurotransmitters dopamine, acetylcholine, norepinephrine, and serotonin and the hormones vasopressin and gonadotropin-releasing hormone. Swedish surgeon Olof Backlund of the Karolinska Hospital in Stockholm has performed two experiments in humans. Each of his patients had severe Parkinson's disease and in each case Backlund grafted tissue from the patient's own adrenal glands, which produce the needed neurotransmitter dopamine. In each case the patients reportedly needed less L-dopa after their grafting operations, but neither patient was able to go without L-dopa entirely. The Swedish scientists plan to continue their work with human patients.

No one is anywhere near ready to try brain grafts to correct human senility, but there is evidence that grafts can correct some of the normal changes that occur in aging rat brains. For example, old rats are not very good at balancing themselves on a wooden pole suspended between two platforms. "Most aged rats have impaired performances. They slip off the pole and they cannot correct themselves when they start to lose their balance," says Bjorklund. The old rats lose their ability to run along the bar because they lose some of their ability to make dopamine. When Bjorklund gave these old rats grafts of brain tissue that produce dopamine, they were once again able to run along the bar.

Grafts can improve rats' memories.

Bjorklund has learned that brain grafts can also correct induced memory impairment in rats that were devised to mimic what seems to occur in Alzheimer's disease. A part of the cortex, the hippocampus, seems to play a role in memory formation. For example, rats normally can learn a certain kind of T-maze within 2 weeks so that they are 100 percent accurate. If researchers damage the rats' septum, which feeds cholinergic fibers to the hippocampus, the rats can never learn to do any better than chance on the maze. But if they are given grafts to their septums of tissue that makes acetylcholine, they can learn the maze to 80 percent accuracy. There is, says Bjorklund, a correlation between the degree that the hippocampus is innervated by the graft and the amount of memory that is recovered. But, he notes, "When you look at the individual animals you see that the correlation is not perfect. There are individual animals that have good innervation but poor function. Cholinergic innervation is necessary but not sufficient for recovery of function. Some additional factor seems necessary but what this factor could be we do not know."

The next question is, What about the changes in memory that normally occur with age? Old rats, it is believed, do not have the mental capacity that they did when they were younger. But before researchers can graft younger brain tissue onto the brains of older rats, they first must learn just what the memory deficits in aged rats are, a task Bjorklund and his associates are now engaged in.

Obviously, this research on memory and effects of aging is aimed at eventually enabling investigators to treat patients with Alzheimer's disease, which currently has no treatment. But before anyone can even think of treating humans with acetylcholine-producing grafts, they will need to find a good source of tissue to be grafted. The grafts that are being tried on the Parkinson's patients are a special case. Investigators use the patients' own adrenal gland tissue because it makes dopamine and because people have two adrenal glands and can get by with only one if the other is used as a source of graft tissue. But there is no equivalent of the adrenal gland to supply acetylcholine for Alzheimer's patients. The obvious solution—and one that works well in animals—is to use fetal tissue. But such a solution raises potential ethical questions. "There are only two solutions that are really interesting in the long run," Bjorklund says. The first is to use graft tissue from some other species, such as monkeys. It is possible to graft tissue from one species into the brain of another and have the graft take but the success rate is not as high as it is within a species. Bjorklund and his associates are now trying to increase that success rate with cyclosporin, a drug that has enormously improved the acceptance of transplanted organs.

Another way to get a source of tissue for grafting is to establish cell lines. Perhaps the initial cells for these lines would have to come from human fetuses, but Bjorklund believes that it would be preferable to use fetuses just once to start a cell line. It would even be possible to use cell-sorting techniques to get the cells as pure as possible before grafting and to establish banks of these cells so that donors and recipients can be matched as closely as possible. The techniques for all of these innovations says, Bjorklund, "are there in principle."

—GINA KOLATA