sity of California School of Medicine in San Diego, they found that a factor (or factors) that stimulates the growth of peripheral nerve fibers attained high concentrations in the Gelfoam by 3 to 6 days after it was implanted. This is the same time at which they see good growth of transplanted tissue. The factor appears to be a protein, but it is not identical to nerve growth factor. The Gelfoam extracts may also contain factors that inhibit the growth of some nerve cells, but these have not yet been characterized, Cotman says.

The Hoffer group has evidence for trophic effects in their intraocular transplantation system. If cortex is transplanted after another tissue, such as locus coeruleus, tectum, or cortex itself, the development of the cortex is enhanced. The enhancement involves both an increased number of neurons and larger neuronal size. Hoffer says, "There are trophic influences; one brain area augments the growth of a second. There are a couple of interesting things about the influences. They do not depend on innervation. The increased growth occurs before the fibers grow out. And physical contact is required. I think it may be some nondiffusible chemical factor."

In addition, Björklund and Stenevi, on the basis of their own transplant and other experiments, have suggested that the hippocampus has the capacity of producing a trophic factor that stimulates the growth of both peripheral and central adrenergic neurons. Because they do not see the growth stimulation when the cholinergic nerve tract from the septum to the hippocampus is left intact, they propose that the septal neurons may ordinarily suppress formation of the factor, which would be released only when the tract was damaged.

Neurobiologists hope that identification of trophic factors and a better understanding in general of brain development will eventually lead to more effective treatments for spinal cord or brain injuries, which all too often produce permanent damage. Damaged brain neurons are not supposed to regenerate, or at least they do not form new connections that are sufficiently normal to restore lost functions.

But, researchers postulate, if they can learn how the connections are formed in the first place, they might be able to reverse the damage. One day perhaps, older brain tissue may be induced to form appropriate new connections just as the transplanted fetal tissue does. Cotman, for one, sounds an optimistic note, "The brain has some remarkable regrowing properties and we are just beginning to see its capacity to restore lost connections."—JEAN L. MARX

Grafts Correct Brain Damage

In experiments with rats and monkeys brain grafting works surprisingly well; human testing has begun

About 2 months ago, physicians at the Karolinska Hospital in Stockholm tried an unprecedented medical experiment—the first transplant of tissue into a human brain. The patient was a man so seriously affected by Parkinson's disease that, without medication, he simply could not move. He agreed to the operation, and the hospital's ethics board gave its permission. The procedure is one that works in rats but has not been extensively tested in other animals.

Neurosurgeon Olof Backlund and histologists Lars Olson and Aki Seiger first removed about two-thirds of the patient's adrenal medulla, which makes dopamine as a minor product. Then they transplanted this adrenal gland tissue directly into the caudate nucleus in the man's brain. There, they hoped, the tissue would grow and produce dopamine.

No one knew quite what to expect. Olson recalls that he and the other Swedish scientists were somewhat relieved when they saw "no immediate or dramatic symptoms when [the patient] woke up. If anything, he was somewhat better." Although, according to Olson, the outcome of the experiment cannot yet be fully evaluated, the man does seem to require less medication—80 to 85 percent of the amount of L-dopa he previously needed. Says Olson, "There was a slight improvement, but nothing sensational." The Swedish scientists are encouraged to try more of these transplants, and at least one U.S. researcher, Don Gash of the University of Rochester School of Medicine, predicts that brain transplants will be clinically feasible in this country within 5 to 10 years.

Brain transplants exploit the blood-brain barrier, which is usually considered a hindrance to medical treatments because it prevents many drugs and other substances from reaching the brain. But the blood-brain barrier also keeps cells of the immune system from reaching the brain, making the brain an immunologically privileged site. It is for this reason that brain grafting may be more feasible than grafting in other parts of the body. Brain grafts seem unlikely to be rejected.

Attempts to transplant brain tissue go back at least 50 years, when the French scientist R. May put brain tissue into the anterior chamber of rats' eyes. Only recently, however, have researchers begun to use brain grafts to correct biochemical and behavioral deficits in laboratory animals. Thus far, they have gotten grafts to make the neurotransmitters dopamine, acetylcholine, norepinephrine, and serotonin as well as the hormones vasopressin and gonadotropin-releasing hormone and have corrected brain damage resulting in movement disorders, memory loss, hyperactivity, and over-responsiveness to stimuli in animals. In addition, one group of investigators is now attempting to give blinded animals light perception by grafting retinas or whole eyes directly into the superior colliculus of the brain.

Most of the work on brain transplants involves grafts of tissues that make dopamine. At the back of the researchers' minds is the thought that their work may lead to a treatment for Parkinson's disease, a progressive neurological disorder characterized by tremor, rigidity, and difficulty in initiating movement. The disease is caused by degeneration of the substantia nigra, a major dopamine-producing region of the brain, which supplies dopamine to the caudate nucleus.

Patients with Parkinson's disease usually are treated with L-dopa, which crosses the blood-brain barrier and is converted in the brain to dopamine. But this drug treatment is far from ideal. Because L-dopa arrives at the brain only periodically, just after the drug is taken, the brain does not make dopamine in response to its needs. Investigators have

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shown that it is this irregular supply of L-dopa that causes the on-off effect—patients have difficulty initiating movements and, once they begin a movement, they have trouble stopping it. L-dopa also can cause patients to become psychotic. Worst of all, the drug eventually stops working. William Freed of the National Institute of Mental Health (NIMH) explains that brain grafts offer the possibility of avoiding these problems with L-dopa. "Ultimately, the hope would be to get a graft that interacts with the brain so that the brain gets dopamine according to its needs," Freed says.

Two groups of researchers are working on dopamine-producing grafts. One is a group headed by Richard Jed Wyatt and Freed at NIMH and includes electrophysiologist Barry Hoffer at the University of Colorado, and histologists Olson and Seiger in Stockholm. The other group is headed by Anders Björklund and Ulf Stenevi at the University of Lund and includes animal behaviorists Fred Gage at Lund and Susan Iversen and Stephen Dunnett at the Experimental Psychology Laboratory in Cambridge, England.

Both groups of researchers have concentrated on trying to repair brain lesions in rats that have a form of Parkinson's disease. To produce these lesions, the investigators first destroy the substantia nigra in one-half of a rat's brain. As a result, the animals develop a peculiar behavioral deficit—they walk in circles. If their brains are supplied with dopamine, they no longer rotate.

The NIMH group began by taking substantia nigra tissue from rat fetuses. They transplanted it into the brains of lesioned rats by inserting it in a ventricle—a brain cavity filled with spinal fluid—that is adjacent to the caudate. As a control, they transplanted sciatic nerve tissue, which does not produce dopamine, into the ventricles of some rats.

The result was a 50 percent reduction in the rats' circling after the substantia nigra tissue was grafted but no change after the sciatic nerve grafting. Wyatt explains that this 50 percent reduction is truly an average—some rats stopped circling altogether and some did not stop at all.

As further tests of whether the brain grafts took and produced dopamine, the NIMH group sent the rats' brains to Olson and Seiger for histofluorescence studies, and Hoffer looked at the electrical activity of the grafts under conditions where dopamine should or should not be released. All indications were that the grafts survived and functioned.

William Freed and Richard Wyatt

Rats with a form of Parkinson's disease walk in circles. These rats are hooked up to devices that record how frequently they rotate.

The European group of researchers has done similar experiments with substantia nigra grafts, but their method of grafting is somewhat different; they test rats not just for cessation of circling but also for "sensory neglect." Animals whose substantia nigra is destroyed on one side of the brain will respond less to touch and smell stimuli on one side of the body.

"For the first couple of years of our research, we used pieces of brain cells for the transplants. We put the brain cells on top of the caudate nucleus, and we learned that the recovery of function is different depending on what part of the caudate we reinnervate," says Stenevi. If they put the transplant in the dorsal part of the caudate nucleus, the rats stopped rotating. If they later surgically removed the transplant, the rats started rotating again. In contrast, if they put the graft on the lateral side of the caudate, the rats' sensory-motor defect was relieved.

More recently, Stenevi and Björklund have been injecting 1 to 2 microliters of brain cell suspensions into the rats' brains rather than transplanting solid tissue. With this method, says Stenevi. "We can reinnervate small areas or enormous areas of the brain. We can inject 15 or 20 such suspensions in the same animal to see if we can correct all the neurological deficits."

Both the United States and the European researchers considered the possibility that the reason brain grafting seems to work so well is that the grafts are between inbred strains of rats that are immunologically compatible. But the investigators do not believe immunological compatibility is the secret of their success. Björklund and Stenevi, for example, tried grafting mouse substantia nigra into rats and found that the grafts grew and functioned well. Wyatt, Freed, and their NIMH colleagues Eleanor Spoor and David Sachs transplanted substantia nigra tissue between rat strains that are immunologically incompatible. Once again, the grafts grew and functioned.

If dopamine-producing grafts are to become clinically feasible, some source of tissue other than fetuses must be used. Thus Wyatt, Freed, and their associates decided to try grafts of adrenal tissue. The adrenal medulla, which is in the interior of the adrenal glands, makes dopamine in addition to the major hormones—epinephrine and norepinephrine. Humans have two adrenal glands, located just above the kidneys, but they can live with just one. The adrenals, therefore, could be a convenient source of tissue for transplants. The tissue is readily available, expendable, and if one of a person's own adrenal glands is used as the tissue source, there should be perfect immunological compatibility.

When Wyatt and his colleagues grafted adrenal medulla tissue into rat brains, they got results comparable to when they grafted fetal substantia nigra tissue. Unexpectedly, these investigators found that the grafted adrenal tissue produced proportionately more dopamine and less epinephrine and norepinephrine than it does in its normal site—apparently the graft responds to the brain's needs.

The next step was to try brain grafts in monkeys. The NIMH group, including John Morihisa, Richard Nakamura, and Mortimer Mishkin, destroyed the substantia nigras of seven monkeys. Five received grafts of fetal substantia nigra tissue and two received grafts of their own adrenal medulla tissue. Only one monkey, however, accepted the substantia nigra graft and one accepted the adrenal graft. In the others the grafts simply disappeared. "We couldn't find the grafts. One possibility is that they were washed away with spinal fluid. There is no evidence of rejection, but there is no evidence that the grafts had even been there," Wyatt says. "The reasons why we are having trouble are far from clear.

We are continuing to play with the problem. The fact that the experiment has worked in two monkeys gives us a great deal of hope," he remarks.

Despite his involvement in the human brain graft attempt, Olson thinks it is important to continue experimenting with monkeys in order to learn where to place the grafts in humans. The monkey experiments are quite difficult, however. For one thing, it is difficult to accurately destroy the substantia nigra in monkeys. Then, once the brain lesions are made, says Olson, "the symptoms are hard to quantitate." Finally, monkeys sometimes spontaneously recover from these brain lesions, probably because the substantia nigra was not totally destroyed.

Björklund, Stenevi, and their associates also have been grafting in another area of the brain—the hippocampus—that they believe is just as suitable for these experiments as the caudate nucleus. The hippocampus participates in learning and memory, and there are a number of good behavioral tests for hippocampal damage. In addition, says Gage, "The anatomical structure of the hippocampus is well understood and mapped out. This helps us determine whether the transplants go where we want them to."

When the Swedish researchers produce lesions in the rats' hippocampus, the animals become hyperactive, startle easily, and lose their short-term memory. For example, under ordinary circumstances, a rat can easily learn that it must go to alternate sides of a T maze to get food. But, says Gage, "if you damage the hippocampus, the rats never learn."

After producing these lesions, the investigators selectively transplant fetal nerve cells that make the transmitters acetylcholine, norepinephrine, or seratonin. "We chose those three sorts of tissue because we know something of what those cells do and we know those cells will grow in the hippocampus," says Gage, "Now we are asking if the cells are functional." The hope is that the different sorts of cells will selectively correct different deficits.

So far, Björklund, Stenevi, and Gage, together with Iversen and Dunnett, are finding that when they transplant medial septal cells, which make acetylcholine, the rats' memories are restored—they can learn T mazes, for example. But they are still hyperactive and still startle too easily. When the researchers transplant locus coeruleus cells, which make norepinephrine, the rats are no longer hyperactive, but they still have no short-term memories and an increased startle response.

The work with memory is particularly intriguing because it may bear on the memory loss that occurs with aging and with Alzheimer's disease in particular. Recently, several groups of researchers have found that patients with Alzheimer's disease lack brain acetylcholine. The Swedish research group notes that old rats lose their memories and lack acetylcholine and they are trying to restore aged rats' memories with brain transplants. So far, they know that the transplants survive in old rats, and they are beginning memory tests.

In order to further study the brain's capacity to accept transplants, Gash and his associates John and Celia Sladek are transplanting another kind of tissue into rats—vasopressin-producing tissue from the hypothalamus. Vasopressin is an antidiuretic hormone without which people would have to drink about 10 gallons of water a day. The hormone also acts as a vasoconstrictor and may be necessary for learning and memory.

Brain grafts seem unlikely to be rejected.

Gash and his colleagues are using the Brattleboro rat, which does not make vasopressin and so must drink its weight in water each day, to study the effectiveness of transplants of hypothalamic neurons. When they place the transplant in the third ventricle of the rats' brains, the tissue produces vasopressin and the rats are able to conserve water. The third ventricle is near the normal site for vasopressin-releasing neurons, and Gash says it is essential that the transplants be placed there. "I think the transplanted tissue must make appropriate connections with blood vessels to release vasopressin into the circulation," he says.

Although occasionally people do not make enough vasopressin, Gash's work is not likely to lead to brain grafts for these patients. Vasopressin deficits can be corrected with nasal sprays. "I'm not sure that transplants of vasopressin neurons have any clinical significance per se," Gash says; "our work is a model for studying important factors in brain transplants."

Dorothy Krieger and her colleagues at the Mount Sinai School of Medicine, Columbia University's College of Physicians and Surgeons, and the University of Oxford also have begun doing brain transplants to study how these transplants function. Her group is using a mutant strain of mice that does not make hypothalamic gonadotropin-releasing hormone and so does not make luteinizing hormone and follicle-stimulating hormone. As a consequence of this mutation, males of this strain have immature reproductive organs and small, undescended testes.

Krieger and her associates were able to correct this mutation by transplanting fetal tissue from the preoptic area, which makes gonadotropin-releasing hormone. After the transplant, the mice began making the hormone—although they never made as much as normal mice do—and their testes got larger and descended into their scrotums.

Freed and Wyatt are starting still another sort of grafting experiment that may have clinical significance. They are grafting whole eyes or fetal retinas into the superior colliculus—the part of the brain that receives visual information—of blinded adult rats. They then pass a fiber-optic device through the rat's skull to the grafted eye so that the eye can "see" the outside world.

Raymond Lund and Stephen McLoon of the University of South Carolina have already shown that fetal rat retinas can grow and make neural connections when grafted into the superior colliculus of adult rat brains. When animals are blinded, the neural connections between the eye and the superior colliculus deteriorate, and the only way to make these animals see is to stimulate the superior colliculus directly.

So far, Freed and Wyatt have shown that the grafted eyes respond electrically to light passing through the fiber-optic device that sticks up from the tops of the rats' heads. Now they are conducting behavioral tests to learn if the blinded rats actually perceive the light as light.

Of course, the eye transplants are just as far from clinical applications as the transplants of tissue to the hippocampus. And some investigators question whether even adrenal gland transplants should be attempted on human patients before more animal experiments are done. Hoffer, for one, says that, before trying adrenal transplants for even the most desperate Parkinson's disease patients, "We really need to make it work in monkeys. I realize that monkeys are expensive and hard to get, but when you contemplate clinical research in man, you need a solid basis." But no one, not even Hoffer, who says he tends to be conservative, thinks that brain transplants in humans are forever out of the question.—GINA KOLATA