NERVE REGENERATION

Fifteen years ago most scientists thought that they would never be able to repair severed nerve fibers in the brain and spinal cord. Now it not only looks possible, it may already be happening.

BY JOAN AREHART-TREICHEL

During the first half of the 20th century, scientists knew that severed peripheral nerves in the body could regenerate (regrow new axons to replace the ones that had been cut), and that some of the new axons would hook up with the right nerve or muscle cell and function just as the old axons did. But they had virtually no evidence that such regeneration ever occurs in the central nervous system, nor that they would ever be able to manipulate severed central axons to bring about their repair.

Then in 1950 something remarkable happened. William W. Chambers and William F. Windle of the University of Pennsylvania School of Medicine were looking for the central mechanism in the body that produces fever. They gave a pyrogen (fever-producing substance) to dogs whose spinal cords had been severed. After the treatment, one dog behaved in a most unusual way. Whenever Chambers pressed its bladder, it howled. Because its spinal cord had been severed, it was not supposed to be capable of feeling anything. They removed the dog's cord, stained it and examined it under the microscope. "We couldn't believe it," recalls Windle, who is now with Denison University in Granville, Ohio. "The cord gave evidence of central axon regeneration."

This finding was reported at a meeting of the Philadelphia Neurological Society and received newspaper publicity. In Georgia, the mother of a paraplegic who had been told that her son was going to die, read about it and hounded her doctor until he got in touch with Chambers and Windle and got some of their pyrogen. He administered it to the paralyzed boy who not only survived but, after several months, got out of bed, walked, hunted, fished and danced. Scientists at the National Institutes of Health were so amazed at the boy's recovery that they had him attend a meeting in 1953 and demonstrate his ability to walk. The press made much ado about it and Chambers and Windle received telegrams and letters from all over the world.

Alas, the honeymoon was shortlived. Scientists were not able to use Chambers and Windle's pyrogen to achieve comparable restoration of walking in experimental animals. Researchers once again came to the conclusion that repair of central axons was impossible. They viewed the apparent cure of the Georgia paraplegic as fortuitous.

During the past quarter-century, however, several neuroscientific advances have reversed scientists' earlier skepticism. During the 1950s, for example, nerve axons were found to carry nutrients, suggesting that if they were severed they had the intrinsic machinery for regrowth. During the 1960s, a small group of nerves in the brain, those that make chemical transmitters known as the catecholamines, were found to regenerate and function again perfectly if cut (SN: 10/24/70, p. 37). Here was more proof that central nerve repair was conceivable. Within the last 10 years, scientists have also shown that collateral sprouting occurs, that is, if central nerves are severed, nearby healthy nerves sometimes take over their function for them. This revelation provided still more evidence that central nerve repair was possible or at least that some substitute might be found for severed nerves.

But the strongest evidence that central nerve repair is feasible is now coming to the fore. Much of it was reported last month at the Fourth Biennial Conference on Regeneration of the Central Nervous System held in Hollywood, Fla., and sponsored by the National Paraplegia Foundation and the U.S. Veterans Administration. In fact, some of the evidence from a Soviet scientist, appears to be of monumental importance and may eventually help a small minority of paraplegics walk again.

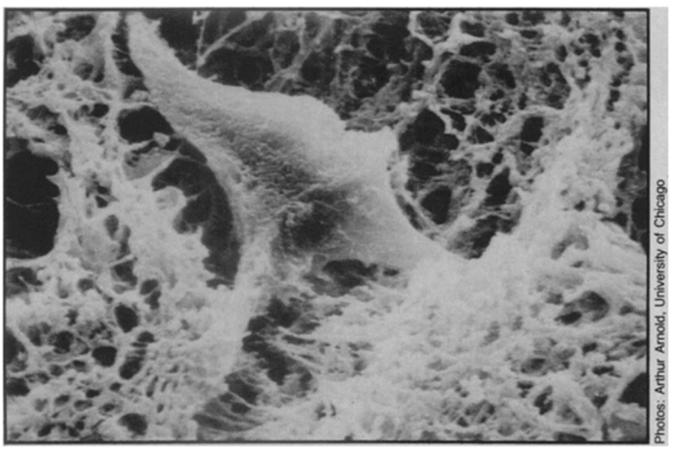
This advance had its inception with Chambers and Windle's work back in 1950. Levon A. Matinian of the Academy of Science in Yerevan, Armenia, read about it and started transecting the spinal cords of rats to see whether a pyrogen or other chemical might block the formation of scar tissue and allow the severed nerves to regrow axons. He worked doggedly and systematically toward this goal for 20 years. Finally in 1973, he hit upon trypsin and several other enzymes that seemed to do the trick. What is more, 40 percent of his 350 rats also recovered from their paralysis and walked.

When American scientists heard about this seemingly miraculous feat, they were reluctant to believe it. Windle visited Matinian's laboratory in 1974 to see for himself and concluded that the work was authentic. The NIH invited Matinian to the United States to discuss his experiments with American researchers. He arrived in May and has made the round of laboratories. American scientists are attempting to confirm his work and should have their results in a year or so.

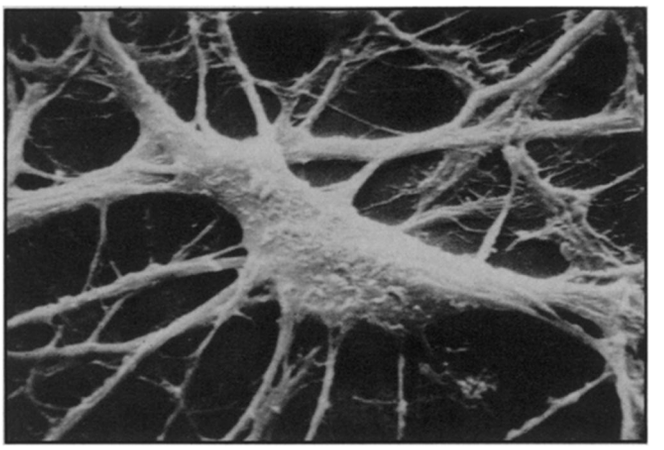
Some of America's leading nerve regeneration experts hail Matinian's research. Windle says, "I think it is an exciting thing, yes." Lloyd Guth of the University of Maryland School of Medicine agrees. "Right now," he says, "we are attempting to confirm Matinian's work in rats." Declares Bernice Grafstein of Cornell University Medical College, "I think it is really remarkable."

These seasoned neuroscientists enter several caveats, however. Grafstein stresses that it must be demonstrated that Matinian's rats are walking again because of regenerated central axons and not because of reflex walking that is due to the severed portion of the spinal cord setting up its own patterns of activity. Less crucial, but also worth answering, she says, is whether Matinian's rats recovered because of regrowth of the cut axons or because of collateral sprouting. Guth, on the other hand, says that it is important to show that Matinian's enzymes bring about the same results in other experimental animals as they do in rats and then to show that the same results can be achieved in people. Even if the technique becomes clinically available, he cautions, it will help only a small minority of patients—those with their spinal cord transected by a knife or bullet wound—not the majority whose cord has received a blow.

Yet even a small number would be a



Central nerve cell from monkey brain, magnified 2,000 times.



Glia, supporting cells interspersed among central nerves.

tremendous feat and a start toward the goal of successfully treating millions of people with damaged central nerves—people for whom there is currently no treatment.

Meanwhile other advances at the basic research level also promise to help scientists learn how to repair damaged central axons:

- Adaptable nerve cells. Central neurons may be more plastic and, hence, more amenable to regeneration than researchers have thought. Scientists used to believe that each nerve makes only one kind of chemical transmitter. Richard P. Bunge of Washington University School of Medicine in St. Louis, and Paul Patterson of Harvard University in Cambridge, have shown that peripheral nerves are adaptable enough to shift gears in certain situations to make another neurotransmitter in addition to the one they usually make. "We didn't have any idea that cells were that adaptable," Bunge says. The challenge now is to show that central nerve cells are equally plastic.
- Nerve cell body crucial. While many researchers have focused on ways to get rid of scarring at the injured nerve site, Kevin Barron of Albany Medical College reports that the nerve cell body will probably also have to be taken into consideration in the repair of central nerves. He has found that when a peripheral nerve is cut, its cell body makes more RNA, the molecule necessary for protein synthesis; yet when a central nerve is slashed, the damaged nerve cell makes less of this crucial molecule.
- Myelin sheath and regeneration. Scientists used to think of the myelin sheath surrounding the nerve axons as simply an insulator. Now there is increasing evidence, notably from the laboratory of Marcus Singer at Case Western Reserve University in Cleveland, that if the myelin is damaged, the axon cannot function, and if the axon is cut, the myelin cannot survive. Singer says "We're tremendously interested in this important connection between the two. And if we uncover more information we may be able to do something salutary in terms of damage to the nervous system."
- Targeting repaired nerves. One of the amazing things about the central nervous system is the precision with which different nerve cells are connected with each other or with muscle cells. If severed nerves are to be repaired, they must be made to grow new axons and also make the axons hook up with the proper target cells. This feat, in turn, depends on discovering how nerves normally recognize their target cells, and Gerald D. Fischbach and his co-workers at Harvard Medical School are one of the groups probing the mechanisms. They have found that when a motor nerve in tissue culture zeroes in on a target muscle cell in that culture, the neuron doesn't go for the muscle cell's acetylcholine receptor but for another spot on the muscle cell. So the acetylcholine receptor at least can be ruled out as one of the things that guides a motor neuron to a muscle cell.
- Why lower animals can regenerate. Since lower animals can regenerate their spinal cords and mammals cannot, some researchers believe that the former holds keys to repair of central axons in people. For instance, the retinal ganglion cells in the goldfish, which go from the eye to the brain, regenerate beautifully if severed and also find their way to the proper target cells. Why? Grafstein and her colleagues have found that there are changes in the protein metabolism of these cells only 24 hours after being cut. She and her team used to believe that such changes only take place three or four days after cutting. "So we will now have to look even earlier for the factors that initiate this regeneration," she says.

Similarly, if one cuts the tail of a salamander, the spinal cord regenerates. Why? There is an internal lining of the spinal cord in all animals and people which first appears in the development of the cord and which then becomes quiescent. But Singer has found that when the salamander's cord regenerates, this inner lining becomes active again and not only forms new nerve cells but lays down little tunnels for nerve fibers to follow in order to reach their proper destination. Clearly then, this lining is crucial in salamanders' central nerve regeneration and probably would be equally vital in repairing peoples' central nerves.

Still other valuable insights that bear on central nerve repair should be coming from American laboratories in the near future. Thus Windle, who kept faith during the many years when most other did not, can happily say, "We are coming closer to the day where we may be able to help individuals with damaged central nerves." □

Nerve repair: The benefactors

When central nerve repair becomes clinically available, it should alleviate incalculable human suffering. The first to profit will be the victims of spinal cord injury—paraplegics and quadraplegics. The National Paraplegia Foundation estimates that 150,000 Americans suffer from spinal cord injury, and about 7,500 new cases occur each year. Most are relatively young persons whose cords have been damaged by accidents and bullet wounds and who must look forward to long lives of frustration and anguish for themselves and their loved ones since there is currently no treatment for them. Such repair also stands to benefit America's three million victims of head injuries, two million victims of stroke and 500,000 multiple sclerosis patients for whom there is no treatment at this time.

Aside from the enormous human benefits, central nerve repair would also save these patients and their families some $10 billion annually, according to a 1975 subcommittee of the National Institute of Neurological, Communicative Disorders and Stroke.