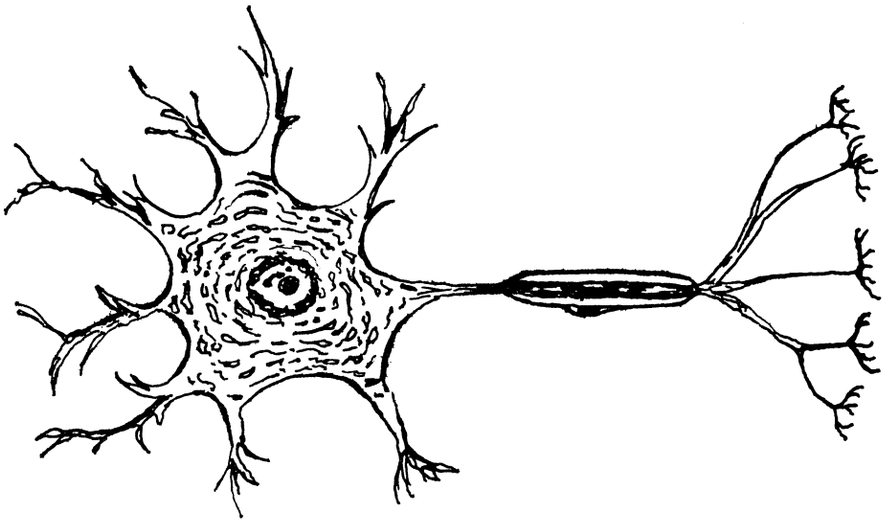
Spinal cord regeneration

Scientists are calling for research on a not-so-impossible dream

by Barbara J. Culliton



The axon, extending from nerve cell body (neuron), conducts impulses.

Hope that a paralyzed human spinal cord can regenerate is not dead.

That hope, generally cast off as cruel dreaming, has been brought cautiously to life by a small corps of scientists. They believe that the time is ripe for applying the knowledge gained from 20 years of fruitful research in biochemistry and molecular biology to problems of central nervous system regeneration in man.

The issue of human spinal cord regeneration is, with good reason, one of the most sensitive subjects in medicine. Because of disease, accidents and war injuries in Vietnam, nearly 200,000 Americans are confined to wheelchairs or bed with partial or total paralysis. Efforts at rehabilitation are expensive, slow and frustratingly unsuccessful in many cases. Occasionally, a physician will announce to his colleagues and the press a dramatic cure of a paralyzed patient. Inevitably, such claims have proved unfounded, earning their maker the scorn of his colleagues for raising hopes that cannot be fulfilled. Clearly, no responsible physician gives a paraplegic reason to believe that he will get up and walk. Indeed, most investigators have considered the probability of spinal cord regeneration so remote that they called research in that direction a waste of time.

With all of this in mind, 22 scientists from a variety of disciplines nevertheless agreed earlier this year to accept an invitation from the National Paraplegia Foundation to assemble in Palm Beach, Fla., for a conference on the Application of New Technology to the Enigma of Central Nervous Regeneration. They came as skeptics. They departed converted to the idea that a tentative reappraisal of the situation was justified. In a summary report, to be published in a forthcoming issue of EXPERIMENTAL NEUROLOGY, they conclude that, "As of today the problem should no longer be considered insoluble."

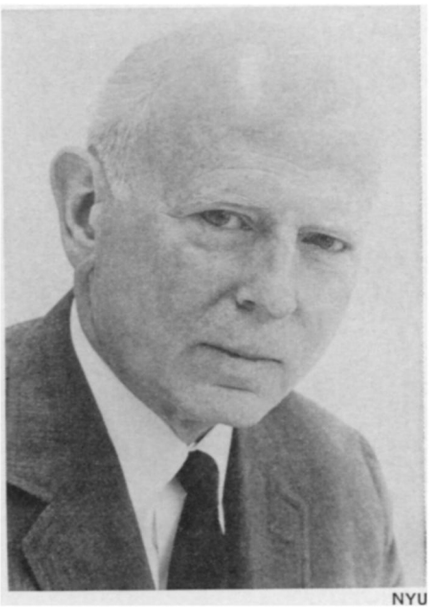
At the same time, they hasten to emphasize that while they are calling for a new research effort, they are by no means suggesting that any practical, medical application looms in the immediate future. Nor do they guarantee even long-range results. But they think it is worth a try. The meeting was called by Dr. William Windle of New York University, a pioneer in studies of human spinal cord regeneration.

Conference participants, from the United States and abroad, represented a wide range of scientific disciplines from neurochemistry to zoology. Focusing their attention exclusively on experimental, fundamental areas of science, they urge investigations of at least four specific phenomena that can now be rationally studied because of recently acquired understanding of cellular behavior. In the 1950's and 1960's such efforts would have been fruitless.

The four areas of increased interest are collateral sprouting, growth of the neuron, neurotrophic interactions and nerve specificities.

■ If peripheral nerve fibers are severed, one of two reactions may occur. The severed fibers may regenerate, or adjacent, intact fibers may develop what are called collateral sprouts to reinnervate the damaged tissue. A similar process is thought to occur in central nervous tissue, including the spinal cord, and scientists have reasoned that if this collateral sprouting could be controlled and directed, nerve function might be restored.

But Dr. Geoffrey Raisman, an anatomist at Oxford University, presents data indicating that collateral sprouting may actually inhibit restitution of severed nerves in the central nervous system. His studies of adult rat tissues show that an injury to nerve fibers does act as a stimulus to their growth and



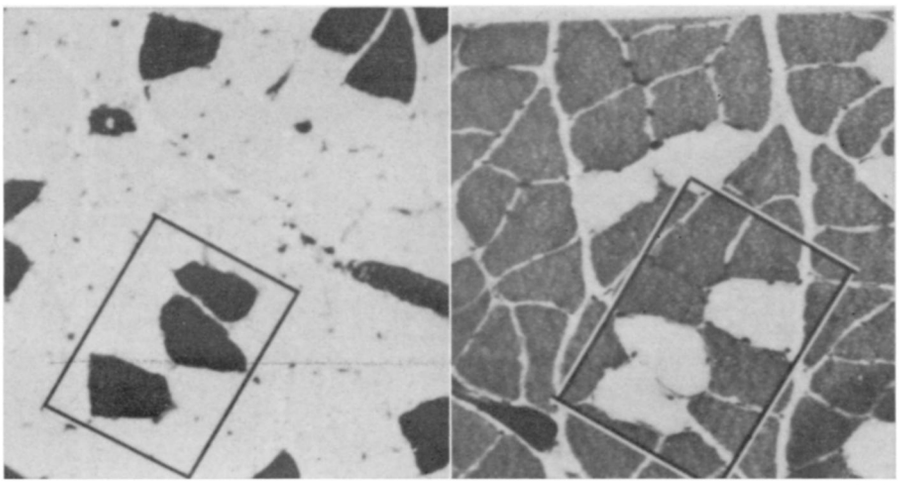
NYU

Dr. Windle: Pioneer in neurology.

to the growth of adjacent nerve axons. But the collateral sprouting or growth of these adjacent axons is nonspecific—collateral sprouts may grow to terminal sites in tissue where they themselves cannot function. In effect, they get in the way of proper regenerating nerve fibers. Further studies of this problem need to be carried out.

■ Studies of rats by Dr. Raisman and others show that mammalian neurons of the central nervous system do have some capacity for regrowth. And studies of fish by Dr. Bernice Grafstein of Cornell University Medical School, and others, demonstrate that these animals have a clear ability to regenerate nervous tissue. Nevertheless it remains possible that regenerating mammalian neurons fail to reestablish functional connections because they are unable to regenerate fully.

Preservation of the neuron or nerve cell body is essential to regrowth. For



Dr. Guth

Fast (r) and slow muscle enzymes are distinguished by staining techniques.

some reason which remains unclear, severing the axon—the long tail that extends from the cell body and conducts nerve signals—often results in death of the nerve cell. Scientists, speculating about the relationship between severing the axon and neuron death postulate that either some feedback mechanism exists between axon and cell body that is vital to neuronal life or the protein loss resulting from axon severing may result in annihilation of the cell.

Still other factors may be implicated in neuron preservation. One is a mechanism functioning locally in the axon that permits sprouting to occur. Another is a set of systems for signaling the neuron to engage in new protein synthesis and for maintaining that synthesis until new nerve cell growth is completed. Understanding of any of these myriad processes could illuminate features of spinal cord regeneration.

■ Neurotrophic interactions, as they are called, refer to a general class of cellular interactions by which a neuron controls or initiates molecular changes in another cell. Experiments conducted by Dr. Stanley Crain and his colleagues at Albert Einstein College of Medicine in the Bronx reveal that the development of organized networks of synoptically connected neurons is not dependent upon prior electrical activity. Studying fetal mouse brain cells in what he calls a drugged cell culture (Novocain was added to the medium to block electrical discharges during the entire period of weeks in culture), he finds that the cells nonetheless form a neural network composed of normal, highly specific connections. After the Novocain is withdrawn, complex, patterned electrical discharges can then occur as in tissue grown in normal culture media. It is tempting, scientists say, to speculate that neurotrophic (chemical) influences may be operating between these neurons as they develop functional CNS relationships.

Among the first investigators to offer evidence supporting this hypothesis was Dr. Marcus Singer of Case Western Reserve University in Cleveland. Addressing the Palm Beach conference, Dr. Singer reported that he and his colleagues believe, from experiments with salamanders with amputed limbs, that the trophic, or regulating, property of neurons derives from a macromolecule or large chemical agent. Dr. Singer's trophic chemical, which has yet to be characterized, is presumed to be nonspecific in its effects—it acts broadly on a variety of cells.

In a somewhat similar vein, neuroanatomist Lloyd Guth of the National Institutes of Health in Bethesda, Md., reported evidence of highly specific trophic influences. In fact, Dr. Guth proposes that one of the trophic actions of a neuron is the regulation of gene expression in the peripheral cells that the neuron innervates.

A series of recent experiments with rat muscle cells supports his hypothesis. There are two main types of muscle fibers. Slow fibers are those that emit continuous electrical signals and perform such functions as maintaining posture. Fast fibers are employed in, for example, raising an arm.

Each type of muscle fiber is innervated by specific nerve fibers, and the biochemical activity of each is associated with the presence of two specific and distinct forms of the contractile protein myosin and its enzyme ATPase. When Dr. Guth and his colleagues cross-innervated slow and fast muscles, sending fast nerves to slow muscle fibers and vice versa, they discovered that the muscle fibers began producing the type of protein and enzyme characteristic of the muscle that nerve normally innervated. Because protein synthesis is known to be controlled by genes, he concludes that the neurons, by some undetermined mechanism, are regulating gene expression in muscle cells.

"It seems eminently worthwhile," he declares, "that a search for both nonspecific and specific trophic interactions between neurons of the adult central nervous system be undertaken."

■ Advances in techniques of tissue culturing allow researchers to probe the specific relationships and trophic influences of neurons on neurons and of neurons on muscles. Studies reported by Dr. Crain are among those of interest in this regard. He has been introducing nerve cells to muscle fiber in culture to investigate the chemical that may be involved in trophic interactions and to observe the results of those interactions. Though data on the former point have yet to accumulate, "We are," he says, "preparing to use a variety of drugs to block postulated trophic factors and thereby gain some insight into their nature."

Although trophic chemicals remain unknown, fascinating observations of interacting nerve and muscle cells have already been recorded. In one case, adult human muscle cells were transferred to a culture medium where, as anticipated, they did not grow at all. Then, by adding mouse fetal spinal cord so that nerve fibers could grow into contact with dormant muscle fibers, the investigators discovered they had created a milieu conducive to muscle regeneration. The mouse fetal spinal cord (nerve fibers) clearly stimulated human muscle cell regeneration.

A series of future experiments are planned to determine whether a similar response occurs if adult human spinal cord or brain tissues are exposed to mouse fetal spinal cord neurons in culture. Likewise, Dr. Crain is attempting to obtain human fetal spinal cord tissue for similar experiments. Fetal tissue is generally known to survive better in culture than does adult tissue, possibly because it is naturally undergoing processes of growth and differentiation that are not common to adult tissue. The implications of this work for spinal cord regeneration in adult human beings are exciting but definitely preliminary.

Indeed, the implications of all the proposed neurobiological research for treatment of paraplegia are speculative and tentative at present. As Dr. Guth observes, however, "In the past, many of us felt that supporting research in human spinal cord regeneration was a case of throwing good money after bad. This is no longer the case. It now seems more sensible to abandon the view that central nervous system regeneration cannot be accomplished in man." □