signal and the effect is cancelled—allowing weaker inputs to have their day.

Although the precise mechanisms of filling-in haven't yet been sorted out, it is clear that filling-in is a widespread phenomenon in the brain. And that, in turn, raises the question of what it is doing there. One obvious answer is that it can allow partial recovery after certain kinds of brain damage. For example, people with gaping holes in their visual fields caused by damage to retina or brain often don't notice, because of filling-in.

That's an interesting insight, but UC San Francisco's Merzenich says filling-in is only part of a much larger story. He characterizes filling-in as a "curious and bizarre phenomenon" that is most interesting for the light it may shed on a more important process: a continuous competitive give-and-take between neurons. In that give-and-take, filling-in is at one far end of the spectrum: If there is a silent spot in the cortex, there is no competition, and weaker connections will certainly fill it in. But in active parts of the brain, the same properties that lead to filling-in will lead to a more subtle plasticity—as conditions change, some connections are strengthened and others weakened, allowing parts of the brain that were formerly thought to be hardwired instead to adapt: in short, to learn.

The kind of competition Merzenich refers to is what lets our brain adapt every day in ways that improve performance. He offers as an example a recent experiment in which he and his colleagues used small vibrators to stimulate the middle finger of monkeys and asked the monkeys to make distinctions between the vibrational frequencies. At the same time, with electrodes implanted in the monkeys' brains, the researchers could monitor neurons in the monkeys' somatosensory cortex. What they found was that as the monkeys improved at the task, the region of the map corresponding to their middle fingers expanded. And Alvaro Pasqual-Leone, at the National Institutes of Health, recently found a similar map expansion in blind people who use one finger to read texts in Braille.

That result, says Brown's Donoghue, shows "you can adjust the organization of your system so it can operate more efficiently when the demand is put on a particular body part." If you need a sensitive touch, the brain expands the area focusing on that sensation. If you need a certain muscle group, as Donoghue and Sanes have observed in recent experiments with monkeys, the brain expands the part of the map devoted to those muscles. "Those adaptive changes, as far as the cortex is concerned, are learning," says Merzenich. And understanding how learning works is one of the ultimate aims of neuroscience—an aim that the latest findings on filling-in and on plasticity can only bring one step closer.

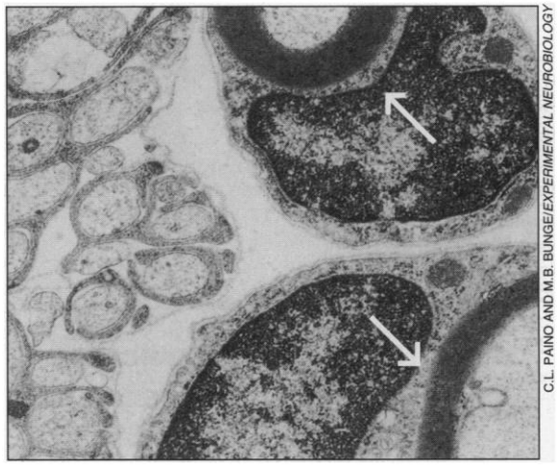
–Marcia Barinaga

SPINAL CORD INJURIES

New Optimism Blooms for Developing Treatments

A few weeks ago, the American Paralysis Association (APA) celebrated its 10th anniversary with a 2-day scientific meeting.* And yes, celebrated is the appropriate word. For while researchers have not found a cure for the spinal cord injuries that paralyze 10,000 Americans every year, progress in a number of diverse areas, ranging from drugs and physical therapy to tissue grafts and genetic engineering, is eliciting new optimism. As recently as a decade ago, most researchers thought that trying to devise treatments that promote recovery from spinal cord injuries was a hopeless task. Now, says Ira Black, chairman of the APA's science advisory council, "There has been a revolution in our views of recovery. We have a whole new armament of therapies to consider."

What accounts for the hopelessness researchers have long felt—and what makes spinal cord injuries so devastating—is the fact that in most mammals the cells of the central nervous system show little evidence of being able to regenerate themselves when they are damaged. That can mean paralysis when the spinal cord's axons, the long fibers that nerve cells send out, are damaged. Since the axons transmit electrical nerve signals from one cell to another, when they're destroyed, the cells can no longer communicate and the body loses all the functions the affected cells control, the ability to move the muscles of the leg, say, or to feel pain and other stimuli.



C.L. PAINO AND M.B. BUNGE/EXPERIMENTAL NEUROBIOLOGY

Insulating axons. Two myelinated axons *(arrows)* with their Schwann cells in a Schwann cell spinal graft.

But about 10 years ago, Albert Aguayo and his colleagues at McGill University in Montreal stunned the world of spinal cord research by showing that in the rat, axons could indeed regrow in the central nervous system. Of course, axon regeneration by itself is not enough to cure paralysis, since the nerves must also reconnect correctly to restore function, but the results provided a spark of hope in a depressed field. Since then, there has been an intensive effort to improve on Aguayo's effort by understanding what substances in the body inhibit or encourage axon regeneration. For example, the growing understanding of one protein in particular, nerve growth factor (NGF), has dramatically changed the field's thinking. But the use of molecular biology to produce NGF is only one among a variety of strategies designed to overcome—or prevent—the devastating changes in life that human beings experience after injuries to their spinal cords.

Molecular biology to the fore

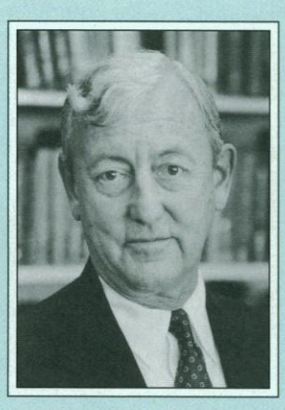
One very promising cutting-edge approach exploits genetically modified cells that can produce healing proteins such as NGF on their own. Fred Gage of the University of California, San Diego, has engineered fibroblast cells to express nerve growth factor and other trophic factors. And in a recent experiment, he's transplanted a collagen gel suffused with such cells into rat spinal cords. The result: Axons grew into and out of the gel, apparently making correct contact with their target cells, Gage reports. Still to be determined, he cautions, is whether such nerve regeneration brings with it functional recovery. Other researchers, meanwhile, are working on a method that uses the herpes virus to integrate growth factor genes directly into damaged nerve cells.

Not all the effort in the molecular biology of spinal cord research is on growth factors. In fact, many feel that the work on so-called inhibitory proteins is the most exciting in the field. Many nerve cells are surrounded by a membranous layer of insulation known as the myelin sheath, and a few years ago, Martin Schwab and his colleagues at the University of Zurich, in Switzerland, discovered that two proteins, apparently present only in the myelin sheath in the mammalian

*"Recovery of Function: The Challenge of Spinal Cord Injury," 16 and 17 September, UMDNJ-Robert Wood Johnson Medical School, Piscataway, New Jersey.

Unorthodox Treatment Stirs Controversy

When researchers and physicians gathered in Piscataway, New Jersey, last month for a meeting marking the 10th anniversary of the American Paralysis Association (APA), one controversial researcher involved in efforts to repair spinal cord injuries—a major topic of the meeting (see page 218)—was not among them. To those who know Harry Goldsmith, a general surgeon at Boston University Medical Center, that comes as no surprise. As even he concedes: "I've always been out of the mainstream. I'm not a member of the club." If he had turned up, Goldsmith might have found himself the object of considerable attention from his colleagues, although perhaps not the kind of attention he desires.



Surgeon Harry Goldsmith

His innovative and unorthodox surgical approach to treating spinal cord injuries—and the fact that he has already begun tests on paralyzed human patients—has stirred up the field in recent weeks. "That's really crazy," says neuroscientist Martin Schwab of the University of Zurich about the human trials. "The experimental data that have been produced are not convincing to my mind."

Schwab was referring to the data Goldsmith has obtained in experiments designed to test whether attaching omentum tissue to damaged spinal cords can facilitate their repair. The omentum is an apron of tissue, rich in blood vessels, that normally resides in the mammalian abdominal cavity, where it provides circulation to the intestines. In the 1970s, Goldsmith developed a surgical treatment for stroke patients in which a segment of omentum tissue is partially detached and, by patching pieces together, lengthened until it can be tunneled under the skin to the skull, where it is sutured to the brain with one end still attached to the abdomen. Once attached, explains Goldsmith, the omentum's blood vessels grow into the brain and provide a steady supply of blood from the abdomen.

Goldsmith didn't stop there. He and the handful of other researchers studying the omentum found that the tissue secretes a number of chemicals, including some still-unidentified nerve growth factors. Moreover, Goldsmith grew interested in the omentum's remarkable ability to soak up the edema fluids released from injured blood vessels. This is extremely useful, he believes, because the pressure exerted by edema can damage nerve cells. A substance in the edema fluids, called fibrinogen, can also lead to the formation of scar tissue that prevents nerve regeneration, Goldsmith says. Armed with these facts, he decided to test whether connecting omentum tissue to the site of spinal cord damage would be beneficial.

Starting in the early 1980s, he performed the procedure on hundreds of cats with promising results, says Goldsmith. He cites, for example, a 1985 study in the journal *Paraplegia*, which he says shows that the omentum procedure can improve the condition of cats with spinal cord injuries similar to those of humans. When the operation was performed within 3 hours of the injury, five of the 11 cats recovered some walking ability, he reported, compared to almost no improvement in a control group of 11 cats. Although another group of 14 cats that underwent the omentum procedure 6 to 8 hours after the cord was traumatized showed no improvement, Goldsmith was sufficiently encouraged to test the procedure on humans. After gaining approval from a Boston University institutional review board, he conducted the first of a dozen planned operations in June.

Schwab and Goldsmith's other critics, many of whom are on the APA science advisory council, argue not only that the move to human trials is premature, but that Goldsmith's own results suggest that it may not work. The reason? Goldsmith is testing his omentum procedure on patients who have had spinal cord injuries for months or years, yet the procedure apparently didn't work on cats when it was performed more than a few hours after injury.

Goldsmith retorts: "I don't believe 20 years of research is jumping in [prematurely]. My problem is I've never had a controlled study [on humans] in an American university." He cites numerous peer-reviewed papers on omentum research that he has published, including one just out in the September issue of *Brain Research*. Goldsmith and Jack de la Torre of the University of Ottawa report there that coupling omentum transfer with a collagen "bridge" allows axons to regrow across the transected spinal cords of cats and apparently reconnect with appropriate nerve cells. While this technique is different from the one used for the previous cat experiments, and has not been used on any human patients yet, Goldsmith contends that the experiment is further proof of the omentum's therapeutic powers.

He also argues that operations done on human patients abroad, where omentum transposition has gained greater acceptance, provide plenty of justification for moving to human trials. He contends that in China, doctors have performed the omentum procedure on more than 2000 spinal cord patients with good results. His critics remain unpersuaded, however, because the evidence has never appeared in peer-reviewed scientific papers. "He has never been able to document to the scientific community's satisfaction his results," says Janna Jacobs, executive director of the National Spinal Cord Injury Association.

Goldsmith is hoping that his first human trial in this country will finally win over the critics. He has already completed the operations on eight of the 12 patients for which the approval was granted and is hard-pressed to rein in his delight at the early data, which he says shows significant recovery of function. When asked if the results will eliminate the controversial history of his work and satisfy his skeptical colleagues, he confidently answers, "Unquestionably. Forget the past." For now though, the jury of his peers is still out.

–J.T.

central nervous system, inhibit the growth of nerve fibers. By neutralizing the proteins with genetically engineered antibodies, Schwab's lab has produced remarkable results in which axons grow up to 1 millimeter per day. Like other researchers, Schwab is now looking to establish that such regeneration leads to nerve connections that can reduce paralysis. He is also combining the antibody treatment with growth factors, a marriage many find extremely promising. "You inhibit the bad guys and help the good guys," says APA's Black.

Prevention is worth a pound of cure

Not all the new weapons against paralysis are aimed at encouraging axon regeneration—some are drugs designed to prevent a wave of so-called secondary damage that apparently occurs in the hours or days immediately after a spinal cord injury. In 1990, for example, a clinical trial directed by Michael Bracken of the Yale University School of Medicine showed that methylprednisolone, a steroid hormone, minimizes paralysis in some patients if high doses are administered within hours of the spinal cord injury. The drug apparently works, Bracken says, by checking

the breakdown of membranes in dead cells (a process that produces a flood of free radicals, which can kill healthy cells). And for spinal cord injuries, emphasize doctors, saving even a small percentage of the cord's axons can mean the difference between complete paralysis and useful motor function.

Promising as the new treatments are for preventing secondary damage, though, some people are too severely injured to start with to get much benefit from them. And, of course, these drugs can't help people injured long ago. But other drugs under development may be able to restore lost function in neurons that have already been damaged. Take for example a drug called 4-aminopyridine (4-AP), which is now going into the first clinical trials in human patients. As Keith Hayes, a clinical neurophysiologist at the University of Western Ontario in Canada, explains: "Until recently, paralysis and weakness were thought [to be] due only to physical damage to axons. But some of the paralysis may be due to the loss of insulation—the myelin." When the myelin sheet is damaged, adds Hayes, potassium channels on the nerve cells are exposed and ions flow out, creating a "short-circuit" that prevents nerve impulses from being transmitted normally. 4-AP helps restore the conductivity of those naked cells by blocking the channels.

"There has been a revolution.... We have a whole new armament of therapies to consider."
–Ira Black

Transplanting the cure

Other researchers are trying to grow the insulation back by transplanting myelin-producing cells known as Schwann cells into the injured area. The idea, says Richard Bunge, the scientific director of the Miami Project to Cure Paralysis, one of the leading groups exploring that approach, is to obtain Schwann cells from paralyzed patients, grow them in culture, and then transplant them into the original patients' spinal cords. And Schwann cells may do much more than just restore myelin coating. Within the past decade, says Bunge, researchers have discovered that the versatile cells secrete substances, such as NGF, that encourage axons to grow.

Another transplant strategy, the use of fetal nerve tissue, also stirred interest at the APA meeting. Either grafts of solid nerve tissue or an injected slurry of fetal nerve cells restored, on average, 40% of lost motor function to cats paralyzed by contusion-type spinal injuries; some even regained near-normal walking ability, reported Paul Reier of the University of Florida Brain Institute and Douglas Anderson of the Veterans Affairs Medical Center in Cincinnati. Their study expands on earlier fetal tissue work in rats and is considered significant because the animal model used by Reier and Anderson strongly mimics the damage most often seen in human spinal cord injuries.

The fetal tissue grafts apparently don't work the way the researchers expected, however. The original rationale for the experiment, says Anderson, was that the fetal nerve tissue might actually form new functioning nerve cells. But there has been little evidence of that, he says, and he and his colleagues now believe that, like some of the strategies mentioned earlier, the fetal tissue somehow "turns back on" intact fibers that don't conduct or function correctly. Exactly how that happens is still a mystery, admits Anderson.

There's also the possibility that the fetal transplants didn't actually help the animals after all. Researchers like Reier and Anderson have to be careful in interpreting their results, since the evaluation of, say, whether a cat is walking better or not is a subjective test. There are few effective quantitative measures that can test motor function in animal models. Moreover, an intriguing effect called "patterning" keeps experimenters wary about whether their treatments actually work. Research has shown that cats with severed spinal cords can, via a treadmill, be taught to walk, apparently by training local nerves to function without the brain's control. Indeed, though the cats cannot balance themselves, some investigators are trying to see if patterning can help human spinal cord patients. Anderson doesn't think that patterning explains his cats' improvement, however, because he tried to minimize the effect by evaluating the cats only once a week.

But the fetal tissue work may have a more important hitch: While such research can be helpful in elucidating the basic science of spinal cord injury, abortion politics may prevent the technique from progressing past cats. The federal government, for example, refuses to fund any experiments involving transplants of fetal tissue into humans.

Rapid growth in sight

Even though researchers have made dramatic progress within the past decade of spinal cord research, they caution that numerous obstacles must be overcome before a cure for a paralysis rises above the horizon. First off, the majority of spinal cord research is still in test tubes and animal models, not humans. "We have no miracles yet," warns Bunge. "This is a field in its infancy," agrees Black. But like infants at many stages of their development, spinal cord research is showing signs of rapid growth.

–John Travis

PALEOCLIMATOLOGY

A Revisionist Timetable for The Ice Ages

In terms of sheer mass, there's no contest. In one corner, there's a land-based record of ice age climates that takes the form of a single carbonate cylinder about the size of the cardboard tube in a roll of paper towels. In the other corner, there's the marine record, which draws on the tons of deep-sea mud cored around the world during the past 20 years. But a group of researchers argues in this issue of *Science* (pp. 255 and 284) that the lone continental record, drilled from a wall of calcite in Devil's Hole, Nevada, is enough to unseat the conventional wisdom about the causes of the ice ages.

That conventional wisdom was established about 10 years ago, when the timing of the deep-sea record seemed to confirm an idea proposed 50 years ago by the Serbian astronomer Milutin Milankovitch: that the great ice sheets waxed and waned in response to the changing distribution of sunlight as Earth's spin axis wiggled and wobbled and its orbit stretched and squeezed over tens of thousands of years. But after analyzing the Devil's Hole timetable of the ice ages, says hydrogeologist Isaac Winograd of the U.S. Geological Survey in Reston, Virginia, "we just found no support" for the influence of orbital variations. Winograd first raised that possibility 4 years ago, but now, drawing on a longer, better dated core and on other climate records, Winograd thinks he's got powerful ammunition against the orbital theory.

Few other climatologists are ready to abandon their interpretation of the marine record and accept Winograd's conclusion that the ice ages, far from being driven by external factors, result solely from an internal oscillation in the climate system. "It's premature," says paleoclimatologist Thomas Crowley of Applied Research Corp. in College Station. Some think the Devil's Hole record itself is suspect, but Crowley and others agree with Lawrence Edwards of the University of Minnesota, who calls the record "an exciting, fantastic data set." Perhaps both records are valid, they say; the records seem to disagree because they tap into different parts of a climate system that is far more complex than had been hoped.

The reason a single stick of carbonate has received all this attention is the unique resource it contains: a precisely dated continental climate record of the past 600,000 years. The record was deposited from ground water, which carried a measure of air tem-