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Paradigm Shift

Broken spinal cords can't be fixed, the dogma said. UTMB researchers are proving that belief false and aiming to help the paralyzed feel, walk and lose their chronic pain.

BY JIM KELLY

In one of the oldest medical texts ever discovered, the 3,600-year-old Edwin Smith Surgical Papyrus, an ancient Egyptian physician describes a patient who, falling downward head first, caused one vertebra to crush into the next. The man couldn't speak, move, or feel his arms and legs. This, said the doctor, was "an ailment not to be treated."

Thirty-six centuries later, despite substantial advances in basic science and clinical care, medicine's ability to restore the sensation and control lost in traumatic spinal cord injury has changed very little. Since World War II, doctors have learned to extend the average post-injury life expectancy of most patients with spinal cord damage from about three months to about thirty-five years. But in helping those same patients recover lost function, the doctors have had minimal success. In fact, for most of the 20th century research into the repair and restoration of injured spinal cords seemed like a dead end.

Scientists knew that, unlike most of the body's cells, the neurons of the spinal cord (and those of the brain, its partner in the central nervous system) didn't reproduce to replace those neurons lost as a result of injury. They also knew that in the spinal cord, the thin fibers that stretch out from nerve cell bodies to carry signals over long distances—known as axons—didn't seem to grow back after being cut. And they were sure that even if such regrowth could be brought about, it would be impossible to guide its course to restore the intricate pathways by which the spinal cord routes orders to the muscles, sends pain signals to the brain, and helps supervise such vital involuntary activities as breathing, heartbeat, and digestion.

"The dogma was that the central nervous system cannot regenerate, that it's a hard-wired system like a computer and it's too complicated to repair," says UTMB neuroscientist Claire Hulsebosch, a slim, brown-haired woman in her early fifties. "There are a whole lot of researchers my age who heard this over and over again."

Hulsebosch smiles as she says this, a look of ironic satisfaction on her face. The reason is simple: the dogma she's describing, which dominated thinking about brain and spinal cord injury for so long, has been overturned—and she and a small group of UTMB colleagues have come out on the winning side of a revolution in neuroscience.

Hulsebosch and the other researchers studying spinal cord injury at UTMB—David McAdoo, Danxia Liu, Olivera Nestic, Regino Perez-Polo, Karin Westlund High, and Ping Wu—have been lucky enough to take part in one of those rare paradigm shifts: critical periods in the history of science when one way of seeing things gives way to another and accomplishments previously considered unattainable suddenly become possibilities. Over the past decade and a half, discoveries by this group and their colleagues elsewhere have helped bring into focus a whole new world of spinal cord research.

They've found that some nerve fibers actually do grow back after spinal cord injury, and they've examined the implications of that regeneration both for recovery of function and the creation of chronic pain. They've started to map the cascade of self-destructive biochemical reactions that follows severe spinal cord trauma, looking for ways to interrupt the process and preserve the large number of nerve cells that normally die as an indirect result of injury. They've developed the first successful technique for transforming fetal neural stem cells into neurons, giving hope that these neurons can be used to replace nerve cells killed by spinal trauma. And they've worked to create new surgical methods to restore lost functions and reduce chronic pain, collaborating with clinicians on campus, in Houston's Texas Medical Center, and elsewhere to speed the translation of research into help for paralyzed patients.

"At UTMB, we've been challenging dogma about spinal cord injury for years," Hulsebosch says. "It's funny, though. Most people think of Galveston as a place to go play on the beach. They don't connect us with high-caliber neuroscience."

A Neuroscience Mecca

Oddly enough, there's a direct link between that beachside location and UTMB's development into a hotbed for spinal cord injury research. UTMB's island setting inspired the 1969 creation of its Marine Biomedical Institute (MBI), whose juxtaposition of marine science and medical research has long focused on neurobiological issues. MBI scientists like William Willis and Richard Coggeshall never limited themselves to studying animals that lived in the ocean; their pioneering investigations into nervous system structure, function, and chemistry evolved to include

all sorts of creatures, everything from rats to cats to people. And they were naturally interested in the spinal cord, the structure around which any vertebrate's nerves are organized.

Thus, from the early 1970s on, UTMB was an especially attractive place for students and young researchers inclined toward neuroscience, and spinal cord studies in particular. A network of basic scientists and clinicians formed around the MBI. Some, like Guy Clifton, who worked for the MBI as a medical student and also did a neurosurgery residency at UTMB, left but kept in touch, becoming collaborators with UTMB researchers. Clifton is now chairman of neurosurgery at the UT Health Science Center in Houston and director of the Mission Connect spinal cord injury research group set up by The Institute for Rehabilitation and Research (TIRR), which brings together researchers from UTMB, UT-Houston, Baylor, and Texas A&M. Others, like Regino Perez-Polo, a specialist in neurochemistry and the responses of nerve cells to trauma, found UTMB the ideal environment in which to put down roots and mature as investigators. And still others, like Hulsebosch and Westlund High, came to UTMB as postdoctoral fellows or graduate students and have spent their entire careers here. "Sometimes I tell people, 'When you grow up in Mecca, why would you leave?'" Westlund High says.

A Personal Crusade

When it comes to establishing a strong spinal cord injury research program in this neuroscience "Mecca," one researcher's contribution stands out. Claire Hulsebosch had a personal motivation for challenging spinal cord injury dogma: when she was 14, her 13-year-old brother Lenny was shot in the spine and paralyzed. "When he was in the hospital we were told there was nothing that could be done, and I asked, well, certainly there's research being done?" she recalls. "The doctors said no, there's no research being done. I was shocked—I knew that even for a cancer patient you would say, there's research, and there's hope. But spinal cord injury patients and their families were told, 'I'm sorry, there's no hope.'"

In one way the doctors were right. Although Lenny Hulsebosch accomplished many things in the 34 years between his shooting and his death from a heart attack in 1997—becoming an accountant, learning to scuba dive, founding a wheelchair basket-

ball league—he never walked again. But when his sister went to graduate school, she discovered that it was possible to do research related to spinal cord regeneration, albeit not in animals with actual spines. She received her Ph.D. from the University of Texas at Austin for work on axonal sprouting, the re-growth of severed nerve fibers, in marine worms and other invertebrates. These fibers lacked the fatty coating known as myelin, which in vertebrates sheathes longer, thicker nerve fibers and electrically insulates them, enabling nerve signals to travel long distances very quickly. The worms' nerve fibers were so thin that they were invisible except under an electron microscope, then just being introduced as a tool of neuroscience. Mammals and other vertebrates also have “unmyelinated” axons; they use them for carrying pain signals. Hulsebosch believed that scientists might have missed the sprouting of unmyelinated axons in injured mammalian spinal cords because they hadn't been able to see them with light microscopes.

In 1979, she came to UTMB on a National Institutes of Health (NIH) postdoctoral fellowship, drawn by the opportunity to work with Coggeshall, an expert in using the electron microscope to study spinal cord structures. Together, they found that unmyelinated axons did indeed sprout in the injured spinal cords of rats—“like a bush that's just been pruned,” Hulsebosch says. What was more, their injuries had an unexpected effect on the rats' behavior. “We would touch animals with this very fine fishing filament that you could barely feel, and they'd act like it was noxious—withdrawing and trying to bite it,” she says. The rats also seemed to have developed a hypersensitivity to heat and cold. Hulsebosch realized that they were suffering something similar to the chronic pain reported by about 60 percent of human spinal cord injury patients, including her brother. Many said they were so sensitive to touch, heat, and cold that even contact with bed sheets or slight changes in room temperature could cause intense discomfort.

UTMB was a very good place for research related to pain. Then-MBI director Willis had established an internationally known group of pain investigators in Galveston, supported by an NIH program project grant, and Hulsebosch's work on axonal sprouting and chronic pain caused by spinal cord injury fit in well. By 1990, she had earned tenure and developed some

ideas about ways to reduce chronic spinal cord pain in rats, as well as perhaps restoring some motor function. And by the mid-to-late '90s she had embarked on animal experiments involving her technique—implanting cells on the surface of an injured spinal cord to act as “biologic mini-pumps” and generate the neurotransmitter serotonin, which reduces the excitability of pain networks and increases the activity of motor neurons—and was thinking about ways to translate this and other research into clinical applications.

At that time, such thoughts were more and more on the minds of spinal cord injury researchers all over the world. The basic science of spinal cord injury was undergoing a renaissance, thanks to the development of such things as antibody markers, which enabled the mapping of neural networks in unprecedented detail, and the rise of a new generation of creative investigators.

International awareness of spinal cord issues had risen to a new high after actor Christopher Reeve was paralyzed by a fall from his horse in 1995 and embarked on a second career as a high-profile advocate for research on spinal cord repair and regeneration.

Another individual tragedy also had focused local attention and financial resources on spinal cord studies: that of eighteen-year-old Emily Conner, who had broken her neck diving into shallow water in Clear Lake. The daughter of a socially prominent lawyer and a real estate broker, Conner issued a challenge to medical schools in the Houston area, promising to raise a million dollars if they would join a TIRR-sponsored spinal cord injury research partnership intended to foster interdisciplinary cooperation. In 1997 and 1998, with the help of a \$500,000 matching gift from the John S. Dunn Foundation, Conner, her family, and friends raised \$1.4 million, and Mission Connect was born.

From the very beginning, UTMB has been central to the Mission Connect collaboration. “UTMB brought to the table by far and away the most developed spinal cord injury research program in the region,” says Mission Connect director Clifton. “Claire's program had been in existence for fifteen years,” he notes, “and she had incorporated a number of other investigators from the Marine Biomedical Institute and the neurosciences department, and they

were heavily funded.” Through the Shriners Burns Hospital, UTMB also had the only facilities available in the region for spinal cord trauma studies in such large animal models as sheep—studies that are crucial to bridging the gap between small creatures like rats and human beings. Clifton has already begun experiments at UTMB with sheep on a surgical nerve “bypass” to restore bladder function after spinal cord injury, in conjunction with Hulsebosch and Investigational Intensive Care Unit Director Daniel Traber.

An Interdisciplinary Approach

Mission Connect has also brought some significant advantages to UTMB. For one thing, the seed-money support the group makes available to young investigators helped attract stem-cell researcher Ping Wu to Galveston in 2000; in 2002 Wu perfected her recipe for transforming fetal human neural stem cells into neurons, which she and others hope can be used to replace spinal cord neurons killed by trauma.

For another, according to Hulsebosch and Perez-Polo, the collegial environment the group has fostered—through monthly meetings that bring together basic scientists and neurosurgeons to exchange ideas, discuss collaborations, and critique unpublished experimental results—has served as a model for the kind of interdisciplinary consortium that researchers believe will be necessary to accelerate the translation of bench science to treatments for paralyzed individuals.

“We very openly discuss experimental procedures and problems, and it’s developed very nicely,” Perez-Polo says. “It’s really a lot of fun to work together with a large number of people using different approaches to a problem of great clinical relevance. And we take a truly translational approach, going from molecular work to work with tissue culture to rats, all the way to sheep and clinical applications to a human situation. Surgeons are intimately involved with scientists on a very egalitarian and active basis, with a total flow of information on both sides.”

UTMB owes one other debt to Mission Connect. In 1998, the organization funded the experiments that provided early data used to fuel an ambitious ongoing collaboration among Hulsebosch, McAdoo, Perez-Polo, and Westlund High. Now fueled by a \$6.2 million program project grant from the NIH, the researchers have joined forces to find a way to go one

step beyond Hulsebosch’s “mini-pump” solution to existing chronic pain caused by spinal cord injury: they want to stop the pain before it starts, with an intervention soon after trauma that may also preserve some spinal cord function.

“After injury,” Hulsebosch says, smacking her hands together to simulate a traumatic impact, “you have a core of the spinal cord that is injured and dies, and it looks like this.” She holds up two cross-section images of a human spinal cord, indicating a dead area at the center of the one on the left. “Those cells are dead; there’s nothing we can do to bring them back to life. But there’s a huge area next to the initial lesion that’s at risk for continued cell death. If it’s left untreated, this is what you’ll get 60 days after injury: just a rim of tissue that survives.” She points to the right-hand image, a cross-section of the same cord, which now looks like a leaf that’s been ravaged by caterpillars. “You don’t have to be a neuroscientist to look at this and say maybe we can rescue these cells.”

To do that, they are drawing on research begun by McAdoo and Danxia Liu, who started studying the toxic chemical environment of the post-injury spinal cord more than a decade ago. Using the techniques of microdialysis, which McAdoo had refined for work with Willis on the neurochemical messengers that transmit pain, they sampled fluid from injured rat spinal cords with a hollow fiber a little over a fifth of a millimeter in diameter. Their goal was to find out what happened in the spinal cord when, as McAdoo puts it, “you have an injury that smashes a bunch of nerve cells and everything in them comes out.”

What happens is that amino acids like glutamate, which normally function as neurotransmitters, suddenly jumped to concentrations twenty-five and even fifty times higher than normal, “overexciting” receptor molecules in surviving nerve cells and launching processes that led to cell death. “Above normal concentrations, glutamate becomes quite toxic,” McAdoo notes. Understanding the mechanism of this “excitotoxicity” and finding ways of blocking it to preserve nerve cells and prevent the development of chronic pain are the central themes of the partnership.

Like Mission Connect, the UTMB program project functions as a collaborative effort. Hulsebosch focuses on evaluating substances that can interfere with the cascade of cell-killing reactions, using her

expertise studying rats' chronic pain caused by spinal cord injury to determine what cells the substances rescue and how that affects behavior; McAdoo examines the complex biochemical response to those substances; and Perez-Polo, working with new faculty member Olivera Nesic, studies post-trauma changes in the protein-building instructions sent out by cells' genes, looking for the signals involved in the process of apoptosis, or cell suicide. Westlund High, whom Hulsebosch describes as "morphologist extraordinaire," creates and analyzes images of the tissues and cells under study, providing insights based on years of experience studying the structure of neural networks.

The group got off to a fast start, publishing papers in 2001 and 2002 on the role of the inflammatory protein interleukin-1 in cell death after spinal cord injury, the post-spinal injury attenuation of a cell-suicide prevention protein known as Bcl-x, and a 50 percent reduction in gene responses to spinal cord trauma when glutamate action was chemically inhibited. Still, the maze of biochemical pathways leading to post-trauma cell death is incredibly intricate, with a

vast number of unknown connections to other processes. It might seem enough to simply block the action of glutamate, for example, but as McAdoo points out, "Glutamate is everywhere in the central nervous system, and when you block it you get all kinds of unintended side effects."

While there are no easy answers, at least there are answers. And for the first time in decades, they seem to be leading somewhere. In Hulsebosch's view, fully understanding the complexity of the problems posed by spinal cord injury is a necessary step on the road to overcoming them. "One problem with spinal cord research in general is that researchers and clinicians have been so focused on getting the limbs to work and improving walking that they've overlooked other areas like pain and bladder and bowel function," she says. "These areas make a huge difference in quality of life, and these are targetable improvements that we can resolve before we get to locomotion and an overall cure. When you have a huge problem like going to the moon, you break it down into achievable tasks. And relieving chronic pain is an achievable task." ■