Pain, Pain, Go Away

Snipping a nerve pathway in the spinal cord may bring instant relief

By SARAH SIMPSON

Cramps burned in her gut. The pain was crippling, despite generous doses of morphine and other narcotics. By late 1995, Diana Rackley had given up eating solid food. Anytime her colon was called upon to do its job, the pain jumped from excruciating to unbearable.

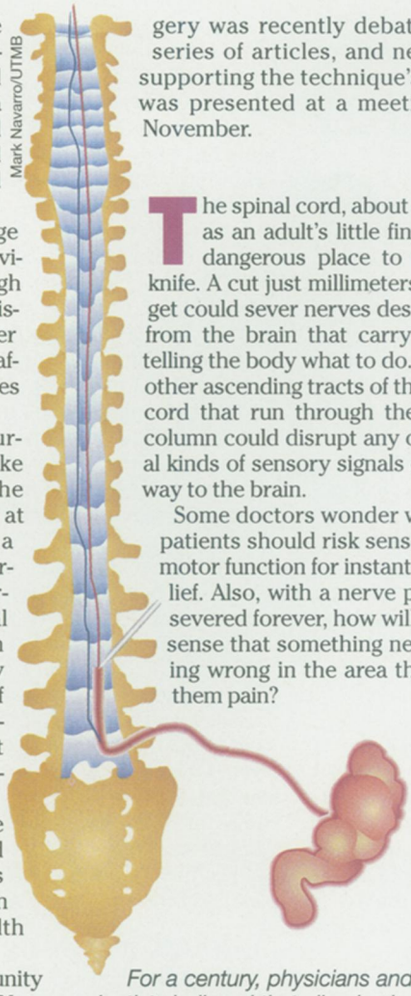
A 39-year-old mother of two teenage children, Rackley had conquered cervical cancer early in 1994—but at a high price. The radiation treatments that disintegrated the cancer also tore into her colon and bladder. Less than 2 years after fighting off a disease that overcomes many, the victory was killing her.

Then, in January 1996, neurosurgeon Haring J.W. Nauta offered to take the pain away. His colleagues at the University of Texas Medical Branch at Galveston had recently discovered a string of nerves that appeared to carry pain messages from the pelvic organs through a section of the spinal cord known as the dorsal column. In rat experiments, one snip of that tiny nerve bundle had stopped most of the pelvic pain messages from reaching the brain. Rackley agreed to let Nauta try to sever the same connection in her lower back.

The day after her surgery, the pelvic pain was virtually gone, and doctors gradually reduced her doses of narcotics. Her pain remained in check until she died last year of health problems unrelated to the surgery.

"I must say that the medical community at large isn't really aware of this," says Nauta, chief of neurosurgery at the Galveston hospital. "Nobody else is doing it, and nobody else has the laboratory backing to feel confident about this." Since telling Rackley's story in the March 1997 JOURNAL OF NEUROSURGERY, Nauta has relieved six other patients of intractable pelvic pain.

Proponents of this new technique argue that it has the potential to aid many people afflicted with enduring pelvic pain, but other physicians aren't so enthusiastic. Critics fear that surgeons and patients alike may be tempted by this seductively simple therapy before enough is known about its side effects. The value of the surgery was recently debated in a series of articles, and new data supporting the technique's safety was presented at a meeting last November.


Mark Navarro/UTMB

For a century, physicians and scientists believed that all pain signals travel up the spinal cord in a nerve bundle called the spinothalamic tract (blue line). New research reveals that cutting a different pathway, called the dorsal column (red line), can relieve pain in pelvic organs, such as the colon.

The spinal cord, about as thick as an adult's little finger, is a dangerous place to wield a knife. A cut just millimeters off target could sever nerves descending from the brain that carry signals telling the body what to do. Cutting other ascending tracts of the spinal cord that run through the dorsal column could disrupt any of several kinds of sensory signals on their way to the brain.

Some doctors wonder whether patients should risk sensory and motor function for instant pain relief. Also, with a nerve pathway severed forever, how will people sense that something new is going wrong in the area that gave them pain?

Some concerns about the procedure arise because, as Nauta acknowledges, his group's surgery challenges a century of medical dogma.

Even the most up-to-date textbooks make no mention of the pain pathway that Nauta has been severing in the dorsal column. Rather, medical professors dub this column "the touch pathway," describing it as a bundle of nerve fibers that route touch and position sensations up the center of the back half of the spinal cord. Pain messages have been thought to travel exclusively along the spinothalamic tract, nerve bundles at the sides of the cord.

Five years ago, however, the Galveston researchers uncovered evidence that the bulk of the pain from the internal organs, or viscera, travels up the overlooked dorsal column, while the spinothalamic tract carries pain messages predominantly from the skin and muscles. Their work paved the way for the spinal surgery that helped Rackley and Nauta's other patients.

In a broad sense, Nauta's approach to reducing pain isn't new at all. Surgeons have been carving up the spinal cord to relieve pain since early in the century. This approach began in 1912, when neurologist William G. Spiller surmised that the tuberculosis tumors pinching the spinal cord of one of his patients must have caused the mysterious numbness on one side of the man's body.

Spiller shared this observation with his colleague Edward Martin, and the pair deliberately cut the spinal cord of another patient to alleviate his intractable pain in both legs. They severed what later became known as the spinothalamic tract.

Since then, surgeons have performed hundreds of these so-called anterolateral cordotomies at various points along the spinal cord. While the incisions have offered at least temporary pain relief for many people, they have often interfered with commands for bladder and bowel control or limb movement.

Surgeons later discovered that it is less invasive and more effective to cut down the center of the cord, where the nerve fibers of the spinothalamic tract cross. This midline myelotomy better alleviates pain plaguing both sides of the body, but it's "basically filleting the cord, cutting it down the middle several inches," Nauta says. The risk of tearing a blood vessel or knocking out other nerve functions is great.

"We've had 100 years or so of this, with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Surgeons have relieved crippling pelvic pain in some cancer patients by severing a pain pathway in the dorsal column (arrow) of the spinal cord, shown here in cross section.

these hugely enthusiastic surgeons cutting this and cutting that, and so far, most of [the techniques] have been eventually dropped," says Patrick Wall, a neurobiologist at St. Thomas' Medical School in London and founder of the journal PAIN. During his half-century of research, Wall says, he's seen the prevalence of pain surgery decrease not only because of the side effects but also because "people became extremely clever with narcotics." These drugs often relieve symptoms without any surgery at all.

But even the most clever drug regimens don't help everyone, says Richard M. Hirshberg. Now retired from St. Joseph Hospital in Houston, Hirshberg is one neurosurgeon who has always believed in using the tricks of his trade to help people distressed by terminal cancer. "These were patients who were in the fetal position, screaming with pain and giving themselves intravenous doses of morphine every 5 minutes," he recalls.

Hirshberg knew that a handful of surgeons doing midline myelotomies in the 1970s had seen patients become free of gut pain even when they aimed to soothe heart or shoulder pain by cutting high up in the neck. That unexpected pelvic relief first made those surgeons suspect that a pathway other than the spinothalamic tract must also transfer pain signals.

Extremely cautious, Hirshberg went after that unknown route with a very small incision, only about half a centimeter long. He also moved his cut down to belly-button level, an area much safer to disturb than the neck, where involuntary breathing controls are at risk.

After surgery, all eight of his previously bedridden patients felt significant pain relief until they died of their cancers. By then, Hirshberg was convinced that a visceral pain pathway lurked somewhere in the dorsal column.

In 1994, Hirshberg took his novel hypothesis and the cord removed from his last patient to William D. Willis, an expert on spinal-cord pain pathways and chairman of anatomy and neuroscience at Galveston. In more than 30 years of research, Willis says, he had never seen anything like this.

"After I talked with Hirshberg—and he seemed to be a very sincere and knowledgeable guy—I called [a mutual colleague] to make sure he wasn't crazy," Willis says.

Upon close inspection of the cord, it turned out that Hirshberg's incision had not even reached into the core, where previous surgeons had expected to find the mysterious pain route. For Karin Westlund High, also at Galveston, that narrowed the search to a small area in the outer, white matter of the cord.

To find the exact pathway, High injected blue dye into a rat's spinal cord at the spot corresponding to Hirshberg's cut. Inside the cord, nerve cells, or neurons, receive messages and relay them along their long fibers, or axons, up various nerve bundles to the brain. The dye in the rat's cord traveled up and down the axons, illuminating the pathway that presumably carries pain signals to the brain from neurons already known to relay signals from pelvic organs.

Meanwhile, Willis' graduate student Elie D. Al-Chaer was searching for neurons in the rats' brains that would react to sensory input from the colon. He found them by stretching the colon with a balloon and irritating it with mustard oil—actions that caused a select group of brain neurons to respond wildly. When he cut the dorsal column, however, Al-Chaer practically abolished the neurons' response.

Hirshberg and the Galveston team published their clinical and laboratory results in 1996. A series of their papers during the next year and funding for the group's work from the National Institutes of Health were enough to convince the researchers' colleague Nauta that it was time to design a surgery for patients. That's when Nauta found Diana Rackley.

"There are millions and millions of articles published every year in scientific journals, but few of them make this jump from the [laboratory] bench to the clinic," says Al-Chaer. "It was for me like a dream come true."

Nauta performs the surgery, which he calls limited myelotomy, by removing a small chunk of protective backbone, no bigger than a postage stamp. With a good view of the cord under a microscope, he uses tiny anatomical landmarks to identify the precise center. He then guides a miniature blade to make a cut 2 mm across the midline and 5 mm deep, being sure to avoid blood vessels.

In his 1997 paper, Nauta noted that Rackley suffered no loss of touch or position sense after her surgery, and he finds the same to be true for his subsequent patients. "We aren't seeing any deficits that weren't there before or that weren't expected as part of the person's original disease," Nauta says.

Others aren't convinced that the surgery is benign. Because Nauta's patients were already so sick, their underlying symptoms might have masked any side effects of their operations, says Karen J. Berkley, a neurophysiologist at Florida State University in Tallahassee. Cutting the dorsal column may rid patients of more than just pain, she suggests. For example, Berkley's current research shows that these fibers also carry messages important to reproductive behaviors in rats.

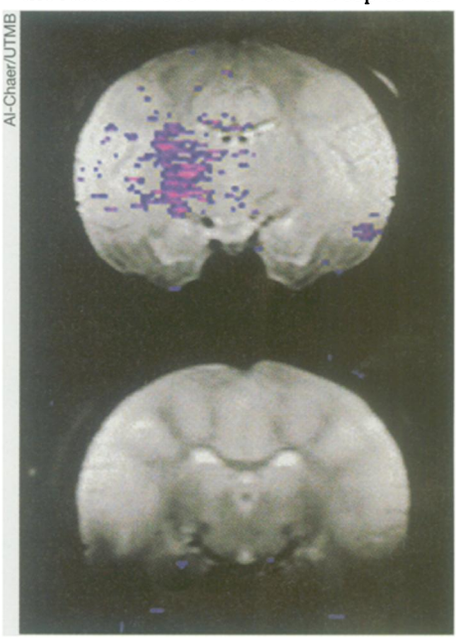
"That's why this idea of dubbing this whole system a visceral pain pathway is so upsetting," Berkley says. "It takes away all these beautiful other functions that it's probably also involved in."

This concern becomes personal when she mentions her husband of 30 years, Mark A. Berkley, who died of pancreatic cancer in 1995. For the 6 previous years, he had suffered tremendous abdominal pain. "That pain had such a big impact on his life that if someone had mentioned something like this—and I weren't his wife—he probably would have done it."

Berkley fears that the dexterity and motor ability her husband needed for his greatest pleasures—skiing, sailing, and hiking—might have been abolished along with the pain.

Before giving in to a surgical fix, Berkley suggests that patients should try a variety of other therapies beyond narcotics. Hobbies, art, massage, exercise, nerve stimulation, hypnosis, biofeedback, and support groups are just a few of the pain diversions that she proposes.

Berkley and others who are skeptical of the new pain pathway held a debate with Willis' group in a series of articles in the Autumn 1998 PAIN FORUM. Despite var-


Al-Chaer/UTMB

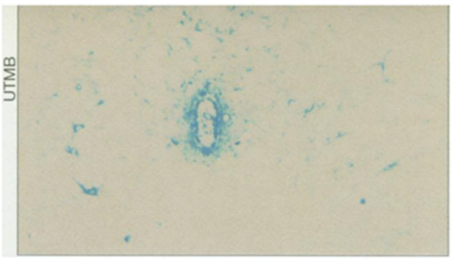
As indicated by magnetic resonance images, a monkey's brain shows a stronger response (purple) to colon irritation before (top) than after (bottom) researchers cut the dorsal column of the animal's spinal cord.

ious concerns, most of the authors say they are convinced of the surgery's utility for dying patients. Even Berkley says that if it had been available, she would have suggested the surgery to her husband during the last 5 months of his life.

The surgeons and researchers at Galveston agree that surgery and the permanent blockage of nerve signals in the dorsal column are not ideal. They have already begun testing ways to block the pathway temporarily by injecting morphine into a specific set of cells in the spinal cord. In the meantime, however, the group is not seeing any side effects from the surgery.

Two years ago, Al-Chaer, who now runs his own laboratory at Galveston, brought in a powerful tool to see whether body control is a casualty of cutting the dorsal column. Magnetic resonance imaging (MRI) allows Al-Chaer and his colleagues to study the effects of the surgery on the whole brain of monkeys instead of just the individual neurons they studied in the rats.

MRI scans of anesthetized monkeys showed certain areas of the animals' brains increasing their activity when the researchers used balloons to stretch the monkeys' colons. Al-Chaer then performed operations similar to those Nauta had conducted on his human patients. The areas that had become activated by colon stretching before the surgery did not do so in subsequent MRI scans, indicating that the surgery had stopped the pain signal.



This cross section of a rat's spinal cord shows nerve cells (blue) clustered around the central area of the spinal cord, known to relay information from pelvic organs. The blue dye traveled up the dorsal column in the cord along the cells' long fibers, illuminating the route that some pain signals take to the brain.

"The surprising and positive outcome of this operation was that there was no loss of function at all in the [four] monkeys we did," says Al-Chaer, who reported this work at the Society for Neuroscience meeting last November in Los Angeles. Now 7 months past their surgery, the monkeys don't suffer diarrhea, constipation, or sensory loss in their legs or tails.

The Galveston group had also wondered whether cutting off pain messages from the colon might block signals that make a person hungry or thirsty, but the researchers see no such problem in the monkeys. "These guys have gone 7 months since their surgery, but they're still gaining weight," Willis says. "Their nutrition hasn't been cut off, even though their brains don't respond to colon distention."

What's more, ongoing studies by other members of the Galveston team show that the dorsal-column pathway may carry pain signals from other organs. The small intestine, pancreas, and esophagus also seem to send their painful cries up the same nerve route as the colon.

"I would be bold enough to say, after looking at four different organs scattered throughout the viscera, that this is going to be a common phenomenon for all of them," says High, who is leading the pancreas research.

Expanding the scope of dorsal column surgery may further fuel the concerns of skeptics. Yet Al-Chaer contends that modern medicine employs many methods simply because they work, even if physicians haven't ruled out all potential side effects. Doctors prescribed aspirin long before all its benefits and risks were known, he says.

"I think it would be a real shame to postpone using [this surgery] until we understand everything," he says. "Using it makes us understand it more and more." □

Technology

Chip uses less DNA and decodes quicker

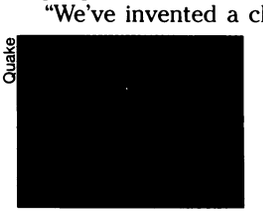
Genetics laboratories nowadays routinely generate DNA "fingerprints." These bar-code–like patterns can help determine paternity or criminal guilt, or provide genetic data for scientific studies.

Conventional analysis requires snipping many copies of a DNA strand into pieces of varying lengths and using electricity to force them through a gel—a process known as electrophoresis. It can take an hour to days for the pieces of DNA to traverse the electrophoretic gel and separate into bands according to their length.

Now, scientists at the California Institute of Technology in Pasadena have demonstrated a new microchip that can make such DNA analyses 100 times faster, while requiring samples of only one-millionth as much genetic material. Channels in the rubbery plastic chip conduct molecules, one by one, past a laser.

The device takes advantage of a method developed earlier this decade to determine the length of DNA fragments tagged with fluorescent dyes. Under laser light, the fragments fluoresce according to their length. Such measurements provide a rapid profile of the sizes of the pieces.

"We've invented a chip-based, single-molecule method for sizing DNA that works on a completely different principle than electrophoresis," says Stephen R. Quake, who led the research team. In the Jan. 5 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, he, Hou-Pu Chou, Charles Spence, and Axel Scherer report fingerprinting a virus' DNA cut into 3,000 pieces—just 28-billionths of a microgram—in 10 minutes.



Laser-lit DNA glows as it travels a groove 5 micrometers wide.

The device might also speed efforts to decipher the entire set of genetic instructions, or genome, of humans or other organisms, the authors say. In particular, it could accelerate mapping, a preliminary step in the process. —*P.W.*

Yellow light warns of nerve-gas peril

A Japanese cult's 1995 nerve-gas attack on the Tokyo subway killed 12 people and injured thousands. The tragic event demonstrated the relative ease of making poison gases, in this case sarin. Detecting these agents poses a formidable challenge.

Researchers at the Johns Hopkins University Applied Physics Laboratory in Laurel, Md., have made a sensor with high sensitivity and unprecedented selectivity for sarin and soman, a related agent, they report in the Jan. 15 ANALYTICAL CHEMISTRY.

Amanda L. Jenkins, O. Manuel Uy, and George M. Murray developed a polymer with which they coat an optical fiber's tip. The coating glows yellow-orange when illuminated by a laser through the fiber. When it encounters and binds to certain chemical derivatives of either of the gases, however, the polymer gives off additional light at a more yellow wavelength.

The polymer was designed to react to versions of the agents that form in water. However, the researchers claim, if the agents are coated with a chemical that alters them in the same manner, the device could also detect them as gases.

The yellow light appears in response to as little as 7 parts per trillion of either agent, well below the concentration at which the compounds have ill effects. Although the sensor requires at least 15 minutes to give a full reading, it produces a detectable response within a minute—"plenty of time for people to put on masks and so on," Murray says. When tested against certain pesticides and other chemical cousins to the nerve agents, the sensor produced no false positives. —*P.W.*