A MATTER OF SOME URGENCY

SCIENTIST CHET DE GROAT HAS REVEALED MUCH OF WHAT WE KNOW ABOUT THE BLADDER

BY ELAINE VITONE

PHOTOGRAPH BY FRANK WALSH

For most of us, spinal cord injury invokes the iconic image of the wheelchair. We assume that what those with impaired mobility want most is to walk again. Our hunch is way off.

In 2004, the Reeve-Irvine Spinal Cord Injury Research Center asked people with spinal cord injuries to rank what would most improve their quality of life. Their answers revealed a powerful theme. Among both quadriplegics and paraplegics, it wasn't mobility that ranked highest but, rather, those aspects of our physiology we shy away from discussing—what even the medical community has traditionally relegated to the catch-bin of "secondary consequences" of spinal cord injury: bladder, bowel, and sexual function.

For 40 years, W. Chet de Groat has devoted his life to studying the sacral nerves, located in the lowest section of the spinal cord and responsible for controlling the autonomic functions of the bladder, bowel, and reproductive organs. A professor of pharmacology and chemical biology and a former director of the pharmacology medical curriculum, he came to Pitt in 1968 and quietly built what remains one of the most prolific laboratories of its kind in the world.

De Groat is 70 years old and stands 6-foot-1 with a full head of white hair. Describing his work, he first breaks down the bladder's complex processes elegantly and succinctly—he's famous for this—and then recites a litany of discoveries, punctuating each with an apology. "Well, I've really beat your ear now," he says. He prefers to put the focus on those he calls his "scientific children and grandchildren" rather than himself.

Humility seems to run in this family. His mentees often say they owe him their careers, and many are now National Institutes of Health–funded researchers, med school department chairs, and biotech entrepreneurs. Worldwide, the de Groat scientific lineage is helping to improve the health and well-being of people suffering from disorders of the bladder.

"Really, we just stumbled upon all of this," de Groat says, recalling how he found his calling in 1966, back when almost nothing was known about the sacral nerves. "We found out that the bladder has a lot of interesting properties."

De Groat was a fellow in Australia, working with neurophysiologists David Curtis and Ronald Ryall to record activity from single neurons in the neck of an anesthetized animal. The trouble was, becasue of the motion of its lungs, those individual cells were tough to hold onto.

One day, after losing yet another neuron, de Groat and Ryall got frustrated. "Let's go to another part of the autonomic system," de Groat suggested. "Something more stable."

Ryall agreed. "And let's get as far away from the lungs as possible."

The good news was that at the bottom of the spinal cord, they could hold on to neurons for hours. The bad news was that there was nothing to record.

The pair found this radio silence odd, and disappointing. But then it occurred to them: Unlike, say, the heart or lungs, the organs at the base of the body are in a resting state for most of the time, except during urination, bowel movements, or sex. Perhaps if they filled the bladder, they thought, those neurons might fire. They tried it, and it worked.

The more de Groat thought about it, the more intrigued he became. Unlike nearly every other organ in the autonomic system, the bladder is controlled voluntarily. Further, babies can't control their bladders, but adults can—which suggested to de Groat that development plays a role. And finally, he realized that bladder research had the potential to ease the suffering associated with a long list of ailments—incontinence, overactive bladder, prostate disease, and spinal cord injury, to name a few.

It would be gratifying work, and as far as he could tell at the time, it wouldn't take long. The system seemed simple: Kidneys make urine, the bladder stores it, and the urethra serves as a reservoir. A sphincter muscle at the top of the urethra acts as a dam. When the sphincter relaxes and the bladder contracts, urine flows out.

But the more de Groat studied the bladder, the more he realized there was more to this "simple" system than he had imagined.

In 1970, de Groat found that in many animal infants, urination demands a prompt. A newborn kitten, for example, requires a lick from its mother to spur the process. Without mom, it will die of renal failure.

Though humans don't require a similar jump-start, we retain the evolutionary legacy of stimulus and response. Hence, when you change junior's diaper, he wastes no time in making you do it all over again. Once the cloth touches him, it's beyond his control.

Most of our autonomic reflexes, like knee jerk, come from the spine, but de Groat's team found that in infants, the urination reflex is an anomaly. A stimulus like the touch of a diaper sends a message up the spinal cord to a region of the brain stem known as the pontine micturition center, which relays the message back down to the bladder, giving it the green light.

Then, when we're toddlers, the brain shifts into voluntary mode. De Groat says it's not clear exactly how this happens, but in adults, the cortex—the part of the brain associated with cognitive control—overrides the reflex.

In the wake of a spinal cord injury, however, the urinary system crashes. At first, the bladder can't empty at all. Then the system comes online again, albeit transformed.

De Groat's team found that in a spinal cord injury, the bladder's wires to the brain are severed forever, and the primitive reflex returns.

In lieu of central nervous system control, the bladder rewires itself using a network of nerves known as silent C fibers. Normally, such nerves would be, well, silent, with only one cue: pain.

After a spinal cord injury, the sphincter and bladder lose their ability to work together. The sphincter doesn't know when to open, and so the bladder works doubly hard to push urine past. As a result, the bladder muscles thicken—hypertrophy, it's called. Pressure backs up to the kidneys, dooming them to fail.

Today, ads for drugs to quiet overactive bladder and treat prostate disease are ubiquitous. The bladder is coming out of the closet. Disorders of the urinary system now warrant recognition as more than a strain on our dignity. For newborn kittens, aging humans, and creatures of all life stages between, when the bladder isn't given its due, the consequences can be debilitating, even deadly.

On a Thursday afternoon in July, de Groat enters his lab in the Thomas E. Starzl Biomedical Science Tower's east wing. The room feels like the inside of a submarine. Knobs and wires jut out from gadgets that line the walls. Behind the oscilloscopes, speakers, and amplifiers, sheets of copper and aluminum shield the lab from noise. Listening to silent nerves is delicate business.

In the center of the room, Research Associate Yongbei Yu stands at a table that holds the star of the show: a tiny, pink balloon less than an inch in diameter. It's the bladder and silent-C-fiber nerves of a rat. A transducer—wired to an amplifier on the wall—measures the pressure inside the bladder.

De Groat offers a peek through the microscope. "In the middle, there's an electrode. The white thing coming over it is the nerve fiber," he says. "Nice preparation, Yongbei. Are you gonna distend it again?"

Yu nods. She presses a few buttons on a small machine that controls two catheters. One fills the bladder with fluid and the other administers compounds—in this case, potential drugs for overactive bladder. The experiment is part of a study with Professor and Chair of Pharmacology and Chemical Biology Bruce Freeman.

Previously, Yu used this same method in collaboration with de Groat to study ATP, the energy source of the cell, which also works as a neurotransmitter and is often involved in pain.

Now, as the bladder expands with fluid, the speakers begin to scratch with static.

"See the baseline widening?" de Groat says, pointing to a stream of line-streaked paper flowing out of the wall. He raises his voice more still, to outdo the now-swelling noise. "This is what happens in your nerves when your bladder fills up," he says, and we watch the waves spill out onto the paper, listen to the neurological ruckus fill the room.

De Groat is highly sought after on the lecture circuit and has won six Golden Apple awards for his teaching prowess. When he attends research talks, he's known to raise a question afterward that amazes speaker and audience alike. "Nobody has ever asked that," they say. "He thinks like a clinician," they add—by all accounts, a rarity for a basic researcher.

Watching him now, ears perking for the amplified utterances of a single, tiny nerve fiber, it's easy to see why he's such a gifted teacher and speaker. Foremost, he's a dedicated listener.

At minimum, it takes a bladder-testing marathon of a conversation just to scratch the surface of the de Groat Lab legacy. He won the Urodynamics Society's Lifetime Achievement Award more than a decade—and 228 papers—ago. Many of the insights that evolved from his early tracing studies 40 years ago have yet to be revised.

Last year, the Christopher and Dana Reeve Foundation honored him with the Reeve-Irvine Research Medal. The foundation's scientific advisory council chair, Oswald Steward, a professor of anatomy and neurobiology at the University of California–Irvine, calls de Groat the world's leading expert in autonomic function and a pioneer in translating basic research to the bedsides of patients suffering from disorders of the bladder.

"Chet has built the story from absolutely the ground up," says Steward. "And his scientific family tree is just truly outstanding—and astounding."

William Steers, chair of urology at the University of Virginia medical school and editor of *The Journal of Urology*, was among the first of many urologists to work in de Groat's lab. After he completed his postdoc in 1989, he joined the initial Viagra trials.

"For those of us in the trenches," Steers says, "where we actually see disorders every day, this training gave us a tremendous advantage—in terms of understanding how these things work, why they go wrong, and how we can treat a range of very common yet poorly understood clinical problems."

Apparently, it was a two-way street. Steers remembers de Groat constantly peppering the MDs in the lab with questions: What do you see in your patients? How does this work?

In the late '80s, de Groat published his hypothesis for easing symptoms of overactive bladder in patients with spinal cord injuries and nervous disorders. His theory involved capsaicin, the stuff in hot peppers that burns your tongue. Just as five-alarm chili feels more like a fire drill than an immolation if you eat enough of it over time, he thought overactive silent C fibers in the bladder might also quiet with capsaicin exposure. Initial studies showed promise: Neonatal rats treated with capsaicin were born immune to pain.

At first, the medical community couldn't get behind the idea. Capsaicin is a neurotoxin, after all. The notion of giving it to patients who already had nerve damage sounded ridiculous.

Then London neurologist Clare Fowler, a longtime friend of de Groat's, gave it a shot. She administered capsaicin solution into the bladders of a group of her patients who had multiple sclerosis and severely hyperactive bladders. And just as Fowler and de Groat had hoped, the capsaicin eased the patients' incontinence symptoms.

Fowler's paper was published in *The Lancet* in 1992; de Groat was a coauthor. Since then, a steady succession of even better treatments using the same nerve-numbing concept have followed. Some of them evolved in de Groat's lab.

De Groat collaborator Michael Chancellor, former director of neurological research at Pitt (now at William Beaumont Hospital in Michigan), was the first to use Botox in the bladder. He went on to treat hundreds of patients with overactive bladder and prostate problems and taught doctors around the world his technique. Patients respond very well, he reports. Some have significantly fewer symptoms. "And some are dry," Chancellor says.

"What's really cool is how long it lasts. In the bladder it lasts six to eight months, and in the prostate it lasts a year. That just blew people away."

Chancellor came to Pitt in 1997 as an associate professor of urology interested in developing a new therapy using muscle stem cells. He thought of stress urinary incontinence (SUI) in women—a disorder in which childbirth damages nerves in the bladder, later causing accidents when far lesser strains, like sneezes or laughter, build pressure in the abdomen. Chancellor wondered: Could stem cells be cultured and injected into the neck of the bladder to relieve SUI symptoms?

"Chet said, 'Hey, run with it,'" he says. "I was able to bounce ideas off of him, hook up with cell biologists in his lab to figure out the models."

Chancellor earned multiple NIH grants for the work, then founded Cook MyoSite, a private firm now conducting FDA-approved trials testing the SUI bladder treatment.

Says Chancellor, "I was only able to do this by the grace of Chet."

The de Groat Lab also aims to understand pain. To this end, Research Assistant Professor of Pharmacology and Chemical Biology Adrian Sculptoreanu has been studying capsaicin receptors at the single-cell level for a decade. "It's like fishing," he says. "It takes a lot of patience."

His perseverance is paying off. He and de Groat are finding that these receptors can remain permanently active in certain disease states—a mechanism that, they believe, might explain chronic pain.

Naoki Yoshimura, professor of urology, started in de Groat's lab as a research associate in 1991. Now the two are investigating how silent C fibers control the bladder after spinal cord injury. Their hypothesis: Hypertrophy—that thickening of the bladder muscles—increases the expression of nerve growth factor, which may spur growth in those pesky, not-so-silent-anymore C fibers.

Research Assistant Professor of Urology Changfeng Tai came to the de Groat Lab in 1994. Working with Research Assistant Professor James Roppolo, Tai has published multiple papers on the use of electrical stimulation on the skin surface to control silent-C-fiber activity in the bladder. They found that electrical currents both inhibit and inspire bladder activity, depending on the frequency of stimulation and placement of electrodes.

"We're trying to understand the mechanisms," says Tai, "so we can find a noninvasive way to control the bladder that will cause fewer complications for patients."

Tai and Roppolo are working with Johnson & Johnson to test a disposable patch with stimulator, microchip, and batteries included. A Boston-based company also is developing an injectable electrode to be placed along a nerve.

De Groat often supports his mentees and colleagues in launching new projects, even when he doesn't necessarily agree with their hunches. Such was the case when Lori Birder, assistant professor of medicine and pharmacology and chemical biology and a former graduate-student researcher in his lab, returned to Pitt in 1997.

Initially, de Groat wasn't on board with her hypothesis that cells of the urothelium—the lining of the bladder that stretches and contracts to accommodate urine—might be a therapeutic target. According to conventional wisdom, the cells were simply a barrier with no active role in bladder function or sensation.

Nonetheless, de Groat gave her space in his lab and, in 2001, she demonstrated that urothelial cells react to stimuli much like neurons and thus have the potential to intensify pain. These preliminary data yielded multiple NIH-funded studies, several of which de Groat collaborates on. (This magazine ran a story on Birder's work in February 2004, online at pittmed.health.pitt.edu.)

Once de Groat takes you under his wing, says Birder, the relationship never ends. "He keeps up with everybody's careers," she says, "even after they've moved on from his lab, and really considers how he can help them achieve their goals.

"And I've never, ever heard anyone say anything negative about Chet," she adds, echoing a widely held sentiment among de Groat Lab alumni. "It's like they threw the mold away."

By all accounts, urology is very big in Asia. Throughout the region, the bladder gets a lot more respect than it does here. At meetings for various research and clinical societies, it isn't uncommon to see de Groat posing for pictures or dining with dozens of Asian mentees-turned-colleagues.

When Chancellor heard that de Groat was turning 70 this year, he decided to throw a birthday party for him in September at the Pan Pacific Incontinence Society meeting in Taiwan.

"We've built up so many friends—students from Korea, Japan, Taiwan. I figured it'd be a wonderful opportunity. How else are you gonna get all these people together in one room?"

The planning fast took on a life of its own: de Groat baby pictures, birthday toasts in Chinese and Japanese. Pittsburgh Penguins shirts, hamburgers, and pierogies—anything to recall fond memories of times in Pittsburgh.

"Can you imagine that?" says Chancellor, "Sixty people in Taiwan wearing Pirates hats and going crazy with the Terrible Towels!"

To picture it is to see a scientific family reunion, a proud grandfather's dream realized. ■