



PITT DOCTORS ARE DRAMATICALLY CHANGING OUR  
UNDERSTANDING OF THE PANCREAS AND ITS DISEASES

BY ELAINE VITONE

# “TEST MY BLOOD. I’M NOT A DRINKER.”

When she couldn’t fall asleep at night, she’d take long, hot baths, or sit on the couch, hugging her knees and rocking, rocking, rocking. Her relationships suffered. She couldn’t keep a job. It went on like this, with debilitating pangs of pain surging through Rebecca Newman’s left side, for 10 years.

Worst of all, everyone kept telling her it was her fault.

They said she had a benign little nothing of a cyst in her pancreas, a side effect of chronic pancreatitis. They said the pancreatitis was caused by alcoholism. “Test my blood. I’m not a drinker,” she insisted. They called her a liar.

Other times, they told her she was exaggerating the pain or making it up completely—as a ploy for pain pills, or because she was crazy.

Brice Kriebel, recovering from surgery for pancreatic cancer, works on a kit plane in his garage. His 5-year-old son plays in the background.

PHOTOGRAPHY | DEREK WAHILA

The truth was that Newman didn't want shots of morphine in those desperate, late-night trips to the ER, or bottles of Percocet from the pain specialists who passed her around like a hot potato. She just wanted the pain to stop.

The pancreas, that tongue-shaped organ/gland below the stomach that neutralizes stomach acid and produces digestive enzymes, is arguably one of the least understood organs in the body. It's difficult to diagnose and treat, and extremely easy to injure. ("Don't mess with the pancreas" is one of the three cardinal rules for new surgeons, right behind "Eat when you can" and "Sleep when you can.") Historically, pancreatic-disease research has moved at a snail's pace, ever short on funding and enthusiasm.

Eighty out of every 100 pancreatic-cancer patients will not respond to treatment. Their disease occurs in only about 1 percent of the population, and yet it's so formidable that it ranks as the fourth-leading cause of all cancer deaths. Precious few survivors are around to advocate for the cause.

Chronic pancreatitis was long considered a disease of drunks. It was shrouded in shame and mystery, and those old misconceptions endure. It wasn't until 1996 that we knew the real mechanisms behind chronic pancreatitis (a disease in which the pancreas slowly and gradually self-destructs, one painful episode of inflammation at a time) and acute pancreatitis (when the patient suffers a single attack of the inflammation so vicious that sometimes it's even lethal). It all has to do with trypsin, one of more than 30 digestive enzymes produced by the pancreas.

In all of us, trypsin occasionally activates inadvertently inside the pancreas instead of the stomach, but a protective enzyme disables it. However, in pancreatitis patients, trypsin is mutated and therefore impervious to our defenses.

That breakthrough 1996 study, which was published in *Nature Genetics*, was led by David Whitcomb, the University of Pittsburgh's chief of the Division of Gastroenterology, Hepatology and Nutrition; director of the Center for Genomic Studies; and professor of medicine, of cell biology and physiology, and of human genetics. By studying families with hereditary pancreatitis, who make up about 2 percent of all chronic pancreatitis cases, Whitcomb's group identified the first of several individual genes that were found to cause trypsin to doom the pancreas. (This magazine

ran a feature on Whitcomb's discovery in the January 2002 issue. You can find it online at [pittmed.health.pitt.edu](http://pittmed.health.pitt.edu).)

The trypsin insight set in motion a kind of domino effect, with subsequent research gradually shedding light on other inflammatory diseases of the pancreas. Whitcomb's group found that mutations in other molecules that normally protect the pancreas from trypsin also lead to acute pancreatitis. They found that acute pancreatitis leads to chronic pancreatitis, and that any inflammation of the pancreas increases the risk of pancreatic cancer.

They're hunting for patterns using comprehensive databases to chart UPMC pancreatic-disease patients' progress on the molecular level, genetic level, diagnostic level, and treatment level. Gradually, they're discovering how each factor interacts with the next, and how genetic variants change the behavior of the whole organ.

Whitcomb is tall—6' 2"—which seems apropos. He and the division he leads approach diseases of the pancreas in a big-picture, lay-of-the-land sort of way. Although Whitcomb is known internationally as a geneticist, he's a physiologist at heart, trained to see genomics more like a means to an end. He speaks in terms of concepts rather than results, much less interested in talking about the next wave of yet-unpublished studies in the pipeline than the extensive body of work his group has published so far in *The Journal of the American Medical Association*, *Gastroenterology*, among others.

In one new study, Whitcomb and his group are laying to rest for good the myth of the alcoholic patient. Twenty centers studying more than 1,000 chronic-pancreatitis patients recently found that these patients don't drink any more than the rest of the population.

In another study, dubbed "SAPS" for Severe Acute Pancreatitis Study, they're determining why 80 percent of people who come down with acute pancreatitis are in the clear after a couple of days in the hospital while the other 20 percent end up in the ICU fighting for their lives—and what can be done to improve outcomes for the latter.

In other studies, Whitcomb's group is finding that pancreatic cancer and nonhereditary chronic pancreatitis each have many different kinds of causes, and that each cause is too complex to be sleuthed out by looking at a single genetic or environmental factor. Rather, these diseases result from perfect storms of

several genes—many of which are fairly common in the population—combined with environmental factors. So far, they've identified four distinct, complex causes that trigger chronic pancreatitis.

Whitcomb believes that for each perfect storm, a specific condition will cause a specific set of abnormal reactions, each requiring its own therapeutic approach.

"Our suspicion is that the treatment that will help one actually makes the other one worse," he says. "For example in some [pancreatitis patients] we want to reduce the stimulation of the pancreas because the cells that make the enzymes are so sensitive. But in other people we want to stimulate it."

Pitt has come to be known as a leader in the fields of pancreatic-cancer genetics, early



pancreatic-cancer diagnosis, and minimally invasive pancreatic surgery. Members of Whitcomb's division frequently present at the American Gastroenterology Association meetings and literally wrote the book on pancreatic diseases. *Advances in the Diagnosis and Treatment of Pancreatic Diseases*, an issue of *Gastroenterology Clinics*, is due out in June.

Even though diseases of the pancreas are complex, the organ itself is relatively simple. Whitcomb says, "The environmental factors affecting it are simple, the disease process is simple. And, if you have an injury, the inflammation is so intense you know exactly the moment that it started and narrow your number of variables considerably."

Consider the big-picture, Whitcombian view of what's ahead: With fewer variables, our odds of cracking the complex codes for problems that affect the pancreas—like inflammatory disease, severe abdominal pain, and cancer—would be that much better. The lessons learned might then be applied to the same problems as they affect other parts of the body. One insight could lead to another, then another—the dominos tumble down.



**Herbert Zeh (left and above left) and A. James Moser consult on Pancreas Day, which is every Wednesday.**

Last year, a \$3 million renovation doubled the size of the Digestive Disorders Center (DDC) in UPMC Presbyterian. Amid this period of tremendous growth, the gastroenterology division refined its approach to running the center.

In the traditional model, on any given day you'd find patients with different kinds of digestive disorders cycling through. A patient would start by seeing a gastroenterologist, who would then refer her to a chain of additional appointments with a dietitian, a surgeon, a pain specialist, a clinical psychologist, then an oncologist and back—and sometimes even to another gastroenterologist with specialized skills.

In contrast, the DDC is organized so that for each patient, a multidisciplinary team collaborates on a comprehensive plan of attack, following it through in the most time-efficient way possible. They do this by focusing on a different set of complex disorders each day of the week. Wednesday is Pancreas Day.

A. James Moser and Herbert Zeh, who codirect the Pancreatic Cancer Center, hold court here each Wednesday. Both are Pitt assistant professors of surgery. Zeh also codirects the University of Pittsburgh Cancer Institute's GI Oncology Program.

Their temperaments seem to complement one another. Moser brims with optimism, rattling off success stories and beaming about the progress of recent years that UPMC's exceptional, multidisciplinary approach has made possible. He talks about "an embarrassment of riches," with all the talent on hand. "In the last

year, we've been able to bring it together very nicely. It takes a team."

Zeh, who's known by his colleagues for his no-nonsense candor, stresses that the hard facts of pancreatic cancer are just as important as optimism. "This is a devastating disease," he says. "One of my pet peeves is reading articles that overplay what I consider to be modest advances and give people false hope. All of that has to be balanced with a healthy dose of realism."

On an overcast hump day in January, a computer-filled, Mission Control-type office at the DDC is abuzz with the comings and goings of people with patient folders in hand—blue folders for pancreatic cancer cases, manila for pancreatitis. The room is a hive of specialists, nurses, and patient ambassadors—staff members paired with patients to coordinate scheduling for every single test, procedure, and appointment.

Pausing to chat between patients, Adam Slivka, MD/PhD professor of medicine and associate chief for the division, says the DDC's new approach is making everyone's time here more efficient. "A lot of times we don't need to see [patients] first. If we get their tests first, we can get a lot done more quickly. So by the time they come in here, I can say, 'Okay, this is what you have. It's been diagnosed and staged. We generate a game plan and an OR date—boom—all in one office visit. Many patients come from far away, and I think they appreciate that.'"

Down the hall in Exam Room 5, patient Brice Kriebel—a wiry 37-year-old with a yellow

Lance Armstrong Foundation LIVESTRONG wristband—and his wife, LeaAnn Kriebel, are staying late after their appointment to share their story. They're glad to do it, they say, because they've found very little they could relate to in the eight months they've spent surfing the Web since they heard the words "pancreatic cancer," uttered by Kriebel's doctor, Moser.

Kriebel lifts his shirt, revealing a long, curved, purple scar across his abdomen. He talks about how active he was before—he had to be to keep up with his former profession-turned-hobby: dirt-bike racing. "Endurance racing through the woods for like three hours," he says, "in the rain and the mud or whatever, or when it's like 90 degrees out, and you have all that stuff on. I was working out, running my elliptical 40 minutes a day, because I'd planned on racing a lot more this summer. Last time I raced was on Memorial Day [2007]."

The couple exchange a knowing, smiling look—a memory.

"Now we're passing that on to our son," LeeAnn Kriebel says softly.

"He's 5. Just took his training wheels off," says Kriebel, a proud dad.

Kriebel has a lot going for him—the resilience of youth and fitness, the expertise of a vanguard treatment center, a supportive family. Still, he and his wife are aware that pancreatic cancer is notoriously difficult to contain. When it recurs—which it does in 80 percent of cases—it almost always hits the patient somewhere else in the body besides the pancreas. It's a come-up-from-behind killer.

Hoping to improve his odds, Kriebel participated in a study led by Moser, which is testing a series of neoadjuvants—in this case, chemotherapy agents designed to be administered before surgery. The more urgent issue for Kriebel may not be the initial tumor in the pancreas, but another nascent cancer that isn't yet big enough to show up on a CT scan.

Thus far, Kriebel and others have responded well. (Moser will present the study's results to the American Society of Clinical Oncology in June.) Kriebel is down to just two microscopic patches of cancer cells. He's eating almost normally now, putting on weight, and looking forward to heading back to work next week. He shifts in his seat, a restless athlete benched far too long. "I just can't stand sitting and watching TV anymore," he says with a laugh.

Another 37-year-old is waiting in the patient room on the other side of the wall—

## Other times, they told her she was exaggerating the pain or making it up completely—as a ploy for pain pills, or because she was crazy.

Newman, whose life for the past 10 years has seemed every bit the classically tragic pancreatitis case. But there's nothing tragic about her demeanor today as she sits sock-footed on the edge of the exam table.

"I love to brag," she says, glowing.

In March 2007, an ER in Altoona, Pa., referred her here. Soon after, Newman had a novel test that originated at UPMC and that is only available at a handful of centers across the country. The test determined that the cyst on her pancreas was the reason Newman had been in pain all those years, not pancreatitis. In time, her cyst developed into early-stage cancer, and incredibly, the doctors caught it when it was still curable.

"The day I got that test was the luckiest day of my life," says Newman.

In most hospitals, when a CT scan shows that a patient has a pancreatic cyst, the next step is a biopsy, to be analyzed under a microscope—a rather subjective method. A human being decides whether the cells on the slide are inflammatory cells or cancer cells, basing that call purely on looks. Up to 15 percent of the time, the tests are wrong, sending cancer-free patients into dangerous surgery needlessly or cancer patients home thinking they are in the clear.

Sydney Finkelstein, former Pitt professor, came up with a better way. He found that by running biopsies through genetic testing, doctors could spot mutations that allowed them to differentiate between a benign cyst, a precancerous cyst, and a malignant cyst. (Finkelstein left Pitt in 2004 to found RedPath, a company that specializes in molecular-level cancer diagnostics.) Asif Khalid, Pitt assistant professor of medicine, recently completed a seven-center study confirming that detailed DNA analysis significantly improved upon the yield of traditional tests.

Newman shows off the scars from the surgery that cured her.

Instead of one long incision, she has several that are small enough to be covered with Band-Aids. Because her tumor was not too entangled with any major blood vessels, and because it was located in the tail end of the pancreas, Moser was able to perform her surgery laparoscopically. (Such surgery on cysts at the head of the pancreas might be too risky because of its intricate plumbing.) UPMC has performed

more than 100 minimally invasive pancreas surgeries. That's more than any other center in the world, more than surgeons have done on the entire continent of Europe.

Newman's story began with years of unimaginable pain and isolation—the hallmarks of everything wrong with pancreatic-disease treatment. Yet it offers a glimpse of what the future may hold for pancreatic cancer. The crucial step is early detection.

Randall Brand directs the GI Malignancy Early Detection, Diagnosis and Prevention Program. In the coming months, he hopes to resume at Pitt an optical-analysis project he developed at Evanston Northwestern Healthcare with Vadim Backman of Northwestern University. It uses light-scattering spectroscopy.

His colleagues at Northwestern initially found that analyzing light signatures calculated from the reflection of white light on normal-appearing colonic tissue allowed them to predict whether a patient had an advanced polyp or cancer throughout the colon. Brand took the concept a step further and showed in a pilot study that the technology worked for diagnosing pancreatic cancer. It was able to discriminate between patients with and without cancer with 95 percent accuracy.

Zeh and Anna Lokshin, Pitt assistant professor of medicine, hope to launch another study this year in order to develop a blood test for early-stage pancreatic cancer. Using a technology called xMAP, they'll be able to simultaneously measure the quantity of multiple proteins in a given sample, then apply mathematical processes to hunt for patterns. Their pilot study found that by using combinations of proteins together, they could detect cancer with up to 98 percent sensitivity.

One of the big challenges in early-detection research is access to blood from patients with early-stage cancer. For years, Brand has worked hard to foster collaborations to create a large, common pool of samples. He'll be the principal investigator developing a Pancreatic Cancer Reference Set through the National Cancer Institute's Early Detection Research Network.

"We feel very strongly that we need to collaborate and support promising projects whether we're the ones that came up with the idea or not," says Brand. "Because we want to find the answer."

Wednesdays at 4 p.m., Pancreas Day wraps up with a mass exodus to a conference room in UPMC Montefiore for a meeting. It's a production—20-some

people in a darkened room looking at CT scans on one screen, pathology slides on another, and on a third, streaming video of a conference table full of more specialists telecommuting from Hillman Cancer Center. Wednesday is Pancreas Day there, too.

Watching this giant brainstorming session, it's clear why Whitcomb and his colleagues tend to recite the words *multidisciplinary team* like a mantra and punctuate each statement with something to the effect of, "Yeah, but I'm just part of it—you've gotta talk to So-and-So." Chalk this modesty up to the experience of working through so many patients' stories together, from the start, and in real time.

Or, chalk it up to the humbling facts of the diseases they're facing.

"Most patients who have pancreatic cancer will not survive it," says Zeh.

"The toughest part of my job is balancing realism with hope. ... Each patient comes in at a different level, and each one needs something a little different."

For Newman, it's been a matter of sorting out the long-misunderstood conflict inside her, from crazy to cancer to what appears to be cured. What she needed was to redefine optimism completely.

Last October, she celebrated her one-year anniversary working as an administrative assistant for a trucking company whose name she wears on her sweatshirt. It's the longest she's ever held a job.

"With last week's check I started a 401K," she says. "That's something I never thought I'd have."

For Kriebel, it was a matter of gearing up for the hardest endurance race of his life.

What he needed most was to get rolling.

Kriebel and his wife recall the day they came back to the DDC after he'd finished his pre-op trial. They sat in silence, the tension mounting as they waited to find out where they stood.

"That was the longest half-hour of our lives," LeeAnn Kriebel says.

"But Dr. Moser was great," says Kriebel of that heart-pounding moment when the door finally opened, and Moser smiled and very succinctly told him that yes, the cancer had shrunk and was still quite operable. Kriebel was OR-bound.

"He didn't beat around the bush. He just came in the room and said, 'Are you ready?'" ■