His brain just sort of “clicked off,” he says. About 10 years ago, Richard Gurwitz was driving on the interstate outside Atlanta, heading to work. The next thing he knew, he was standing in a ditch next to the highway, and a police officer was shaking him.

“I’m diabetic,” Gurwitz said as he came to. The officer got him some food, then told him how he ended up in the ditch, according to the employees at the McDonald’s nearby—the one Gurwitz went to every workday morning for breakfast. They said Gurwitz stopped at the drive-thru, ordered, then proceeded without paying. They watched him get onto the highway, then back his car into the ditch. But Gurwitz has no recollection of any of that. The last thing he remembers, he was driving on the interstate about five miles before his regular McDonald’s stop. Somehow he was able to traverse those miles, even order breakfast, without knowing what he was doing.
A couple of other times while he was driving his brain clicked off like that, too.

Still Gurwitz, 37, managed to live a fairly normal life with type 1 diabetes. Daily insulin shots enabled him, for the most part, to stabilize his metabolism and stay active. He helps run a Kinko’s in Fort Lauderdale and amuses himself in his free time kayaking in the Everglades looking for wildlife (where he has seen lots of mosquitoes but no alligators). At 5 feet 4, he plays basketball with lots of heart, if not the heft of the big guys. Decades of diabetes have taken their toll, though. He required five laser surgeries on his eyes to preserve his vision. He counts his lucky stars that he hasn’t suffered kidney failure.

Gurwitz figured he would be diabetic all his life. Happily, it looks like he was wrong. In the fall, he underwent an experimental islet cell transplant at the University of Miami. Doctors have met with success with this minimally invasive procedure only recently.

Normally, beta cells within what are known as the islets of Langerhans in the pancreas produce insulin. In people with type 1 diabetes, the islets are destroyed, and their bodies are no longer able to convert food into fuel automatically. Diabetes is the Greek word for siphon, in reference to the unquenchable thirst and hunger met by those who could not process nutrients but only urinate “like the opening of aqueducts,” as Aretaeus of Cappadocia put it. Aretaeus, born in 30 BC, named and described the disease. (“Mellitus,” a Latin word added later to the name, refers to the honey-like smell of urine common among untreated diabetes sufferers.) Until the 1920s, when researchers at the University of Toronto developed insulin therapy, type 1 diabetic patients usually withered away and died, often in their youth.

As an adult, Gurwitz required 58 total units of insulin, administered in two shots each day. Since the islet transplants, he no longer needs those shots; his body now produces enough insulin on its own. He feels great: “I’m like a normal person. I can do anything I want!”

Gurwitz’s good health is great news to the more than one million suffering from type 1 diabetes in this country alone. Yet transplants like his can require two to four pancreases worth of islets, and there aren’t enough donated organs to go around. Researchers at the University of Pittsburgh are closing in on a solution.

Before Rupangi Vasavada, a PhD molecular biologist in Pitt’s Division of Endocrinology and Metabolism, became interested in diabetes, she was studying a gene called PTHrP which scientists now understand is expressed in almost every tissue in the human body. Knockout mice created without PTHrP die very young. In 1996, when Vasavada was working in the lab of Andrew Stewart at Yale University (Stewart is now her division chief at Pitt), she learned that PTHrP is also made by the islets. She wondered what the protein was doing there—if anything. So she genetically modified mice to produce large amounts of PTHrP in the islets. To her surprise, she'd created hypoglycemic mice. Somehow, all of that extra PTHrP had caused an increase in beta-cell mass, spilling insulin into the animals’ blood at a hyper rate. Glucose levels dropped. The opposite happens in diabetic models.

“To us, it was very exciting at the time,” notes Vasavada. She’d found a potential growth factor for beta cells. But how did PTHrP increase beta-cell mass? At this point, she has narrowed the mechanism down to two possibilities: Either PTHrP plays a role in decreasing the normal rate of beta-cell death or the protein affects precursors to beta cells. Her colleagues in the endocrinology division, Adolfo Garcia-Ocana, Karen Takane, Ana Cebrian, Juan Carlos Lopez-Talavera, and Stewart, are pursuing other promising islet growth factors as well.

As they get closer to offering the world a new supply of insulin-producing cells, Gurwitz is likely to be getting ready for his next Everglades trip: strapping the kayak to his truck, settling in behind the wheel—alert and ready for the adventure ahead.
fluorescent markers. With these advances, Drain, now an assistant professor of cell biology and physiology at the University of Pittsburgh, has changed his mind.

These days, the former naysayer is devising some new imaging methods himself. Working with other Pitt researchers, Drain contributes to the development of new therapeutic approaches to diabetes. The group, led by Massimo Trucco, the Hillman Professor of Pediatric Immunology, recently received a $10 million grant from the Juvenile Diabetes Foundation.

In an attempt to cure type 1 diabetes, some researchers have tried to transplant into diabetic patients the islets of Langerhans. Scattered throughout the pancreas, the islets are clumps of cells that secrete insulin and regulate its release. In 1999, researchers successfully transplanted islets for the first time—blood glucose levels in the recipients became normal, although patients had to be placed on a regimen of immunosuppressive drugs. (Trucco’s group recently applied for approval from the Food and Drug Administration to perform the experimental procedure at Pitt. His colleagues and sometime collaborators at the University of Miami are among the handful of clinicians who’ve performed these procedures successfully—see “Wanted: More Islets,” page 8.)

While transplants seem to hold promise, many questions surround them. For example, to achieve normal glucose regulation in the recipient, perhaps three persons’ worth of islets must be transplanted. Why does it take so many islets? Are some of the cells dying after transplantation? Are the cells producing a normal amount of insulin? Is the insulin being released normally in response to glucose? No one knows.

Mouse models, thought the Pitt scientists, might provide answers.

Wouldn’t it be revealing, they thought, to transplant islets into a mouse and then later perform a biopsy of the transplanted islets? They could use a special microscope to measure, in the living cells they had extracted, how much insulin was being produced and released in response to glucose. Better yet, what if they surgically implanted into a mouse a skin flap, with a window for a microscope underneath? They could position the flap so that they could simply pick up the mouse and look directly at the islets (which are transplanted into a transparent pocket that surrounds the kidney). Using a handheld microscope, the scientists could then measure the function of the transplanted islet cells inside the living animal.

A major stumbling block prevented them from doing the experiments. For seven years, scientists had tried to fluorescently label insulin in living cells. Nothing worked.

Drain got to thinking.

Once insulin is made in the cell, it goes to the Golgi apparatus (a protein refining factory). As it leaves the Golgi (in an immature form), it becomes sealed inside a granule, where it remains until it is taken to the cell membrane and released outside the cell.

Once inside the granule, the immature form of insulin matures—part of the protein, called the C peptide, is cut away. Other scientists had tried labeling mature insulin, but found that the labeled insulin no longer functioned normally. Drain thought: Why not label the C peptide instead? The C peptide remains in the sealed granule. Since there is one C peptide for each insulin molecule, researchers would be able to measure the amount of insulin in the granule.

Drain tried the experiment. It worked.

One afternoon in his office, he shows a video of insulin secretion in a living cell. The cell is just beginning to respond to an increase in glucose levels. The cell moves. Its insulin granules move. Some granules head toward the cell membrane. A couple pop out of the cell; the fluorescence abruptly disappears as the granule ruptures, dispersing its contents. “This is as good as it gets,” he says.

“My favorite thing about science is realizing that I’m completely wrong on something I was completely convinced of,” says Drain. He was wrong, he admits, about a picture’s worth.
During an episode of inflammatory bowel disease (IBD), diarrhea and abdominal pain can be so severe that normal daily routines are impossible. IBD can lead to a blocked intestine, intestinal infections, nutritional deficiencies, and other complications.

A 1996 finding from a group of French scientists provided hope for a better understanding of the causes of IBD. In 1996, the French scientists published a paper in Nature showing a link between a region of chromosome 16 and Crohn’s disease (ulcerative colitis and Crohn’s are the two forms of IBD). The paper set in motion an international race to find the first gene for Crohn’s.

Shortly after Richard Duerr, assistant professor of gastroenterology, hepatology, and nutrition at the University of Pittsburgh, heard about the French study, he joined forces with collaborators at the University of Chicago and Johns Hopkins University. Working together, the scientists decided, they would have a better chance of finding genetic causes of IBD, which affects about 2 in every 1,000 people in Western countries.

As collaborators, Duerr and the other scientists would share DNA samples from affected families. Although Pitt has one of the largest collections of IBD DNA samples in North America, with data from 1,700 members of 350 families, far more samples were needed.

“To find human disease genes in a complex trait like inflammatory bowel disease, we need many, many samples. A few hundred families by themselves are generally not enough to find genes,” says Duerr. Joining forces gave Duerr access to samples from an additional 1,500 members of 388 families. When the collaboration formed, each group focused on a different region of the genome. The 1996 discovery linked Crohn’s to chromosome 16, so Duerr’s collaborators in the Windy City began looking for the gene on the implicated region of chromosome 16.

Judy Cho was leading the Chicago effort. One day, she got a phone call out of the blue from a stranger—Gabriel Nuñez, a scientist at the University of Michigan. Nuñez studied a gene called NOD1. He had been looking for genetic sequences that might be similar to NOD1 and found a similar sequence—on chromosome 16. It was in the middle of the region linked to Crohn’s disease. A light bulb went on. Nuñez knew the predominant theory of the cause of IBD: that normal gastrointestinal bacteria somehow stimulate the immune system into a chronic inflammatory response. NOD1 was involved in immune system signaling and bacteria sensing, and this region appeared to be as well. Could the genetic sequence he had found on chromosome 16 be involved in Crohn’s? He learned of Cho’s work on IBD and eventually picked up the phone.

Together, Cho and Nuñez looked more closely at the region of chromosome 16 that Nuñez had identified. Using the collaborative group’s DNA samples, including those from Pitt’s large collection, the two scientists discovered a gene (now called NOD2), which has three different mutations that are significantly more common in people with Crohn’s. At the same time, the French group that had initially reported the chromosome 16 linkage uncovered the same NOD2 mutation. Papers from the two groups, jointly announcing the discovery of the first Crohn’s gene, were published side-by-side in Nature on May 31, 2001.

“This discovery goes beyond the study of Crohn’s disease,” says David Whitcomb, chief of Duerr’s division at Pitt. He speaks admiringly of how the collaborators, using sophisticated statistical genetic techniques, localized the chromosomal regions where individual mutated genes lie, and then, using knowledge of the biology of the disease, identified culprit genes.

“It is likely that the same techniques and methods will be successful in discovering the underlying genetic causes of other complex diseases,” Whitcomb adds.

Since the 2001 discovery of the first Crohn’s gene, other researchers have confirmed the association with Crohn’s. But, only 20–25 percent of those with the disease have any one of the three known mutations. That means other genes are yet to be found.

These days, with the help of a $1.4 million grant from the National Institutes of Health, Duerr is looking for an IBD gene on chromosome 3. He also recently discovered that a region on chromosome 12, which had been previously linked to IBD, seems more related to ulcerative colitis than to Crohn’s. He’s hot on the trail of more IBD genes.