avid Whitcomb had heard the stories of desperation. One woman had two children, 9 and 11, with hereditary pancreatitis, a little known disease. According to their pediatrician, either gallstones or alcoholism caused pancreatitis. The children clearly didn’t have gallstones, so the doctor made a diagnosis that was heartbreaking but that logic seemed to dictate: “Her pediatrician told her that the reason the kids had pancreatitis is that they were sneaking out and drinking,” says Whitcomb. “As a mom, she would see her kids rolled up in pain, vomiting and vomiting, and just crying out for help. These episodes would last for two or three days. What is she going to do?”

Whitcomb, professor of medicine, of cell biology and physiology, and of human genetics at the University of Pittsburgh, knew that the children were not closet alcoholics. Their disease was hereditary; in 1996, he had discovered a gene that caused it. A year later, as he planned the First International Conference on Hereditary Pancreatitis, he wanted the physicians and scientists who attended to hear stories, like the many he had heard,
about living with the illness. He asked two people with hereditary pancreatitis to speak at the scientific meeting.

One of these speakers was Jean Burke (not her real name), whom Whitcomb had visited at home as part of his research. He sat in the audience as Burke told her story to a perfectly silent room:

From the moment my daughter was born, I felt a deep tear in my heart that she would develop pancreatitis. . . . Last March, the inevitable finally happened when we learned she had this disease. . . .

She is five years old, she has blond hair, brown eyes, and she is filled with endless energy. . . . When she is sick, she will always have a stomachache, which terrifies her. It is this disease that she has that scares her. Lately, I have been able to tell her, “Do you remember those wonderful doctors who came out to the house and we met? Well, they are working on something to make you feel better. They are going to help us. They are doing their best.” That helps her, she calms down, and she smiles.

As Burke talked, Whitcomb glanced over his shoulder. In the audience, he recognized people who worked in his own lab or the labs of his collaborators. These researchers had no patient contact though, day in and day out, they moved the study forward. At some point, they may have held a vial of blood from Burke or another study participant. More likely, they’d seen only a minuscule amount of a clear solution derived from blood. Now they had a face and a story associated with the disease. Hearing Burke, it hit home: The hundreds of faces, the hundreds of patients, the hundreds of studies, have successfully enriched understanding for months and sometimes die.

Little else was known about this mysterious disease when Whitcomb came to Pitt in 1991. No one knew, for example, how the digestive enzymes became activated prematurely—not until Whitcomb started looking into it.

He had an idea. He knew of a few, scattered published reports documenting cases where pancreatitis ran in families. The straightforward inheritance pattern indicated that a single gene was causing the disease. If he could locate the gene, he thought he could also locate the protein, encoded by the gene, whose malfunctioning causes the disease. (Other researchers, notably Nancy Wexler with her Huntington’s disease studies, have successfully enriched understanding of hereditary disorders by focusing on afflicted families.)

Then, by looking at how the protein functioned in its normal and mutated states, he hoped to understand the cause of pancreatitis.

“Genetics was the only way that we could imagine to solve this problem,” says Whitcomb.

As far as he knew, he had never seen a patient with hereditary pancreatitis. (Its clinical presentation is identical to that of other types of pancreatitis.) But he had heard that there was a family in Kentucky with the disease. A friend of his, Larry Gates, had a practice there. He called him, but Gates hadn’t come across anyone with hereditary pancreatitis.

Two weeks later, he got a phone call from Gates: “Dave, you won’t believe what happened!” Someone had just walked into Gates’ office and declared, “I have hereditary pancreatitis.”

“How do you know?” Gates asked.

The man took out a scroll and unraveled his family tree, with about 500 people mapped on it.
The generations dated back to the Civil War, so did the mysterious abdominal pain.

“Where do all these people live?” Gates asked. They lived in the surrounding region, and the man was interested in participating in a study to help find the cause of the disease.

Whitcomb called up Gates’ patient. It’s coming up Memorial Day, Whitcomb said. Why don’t we have a family reunion and invite everybody?

Whitcomb, a colleague, and two of his four children headed to Kentucky on Memorial Day, 1995, their car loaded with supplies needed to draw blood. His collaborators from Lexington and Cincinnati brought grills, meat, buns, and the fixings. About 140 people from the invited family came. In between helpings, Whitcomb’s team charted the family history, listened to people’s stories about living with the illness, and collected blood from nearly 100 people.

After his return to Pitt, Whitcomb’s lab studied DNA from the blood samples. Within a year, they had discovered the gene that was mutated in the family members who had the disease. The gene, located on chromosome seven, coded for trypsin.

The pancreas produces about 30 important digestive enzymes, and among these trypsin plays a central role. Trypsinogen (the inactive form of trypsin) becomes activated when it touches the wall of the small intestine. Trypsin then sets to work—going to all the other digestive enzymes, converting the inactive form into the active one.

As a researcher and as a community member, Whitcomb finds that outreach comes naturally to him. Here, he’s shown at home with his “gigantic family,” which includes young adults from his church who stop by each week.

In everyone, trypsin sometimes becomes accidentally activated in the pancreas. If it does, a protective enzyme goes into action. The molecular structure of trypsin is such that there are two parts linked by a connecting chain. The protective enzyme simply cuts the
chain, disabling the trypsin. In the people Whitcomb studied with hereditary pancreatitis, he discovered the chain is mutated, and the protective enzyme is powerless to cut it. There is no way to shut off the accidentally activated trypsin. The trypsin activates all the other digestive enzymes, and they set about breaking down the pancreatic tissue.

Before this finding, the last major breakthrough in pancreatitis had been 100 years earlier, the 1896 discovery that autodigestion caused the disease rather than infection. Whitcomb had pinpointed a precise cause. The study was published in *Nature Genetics* on October 14, 1996. He had the first page of the article framed; it hangs beside his office door, where his eyes fall on it every time he leaves the office.

Since the 1996 discovery, Whitcomb has sought out other families with hereditary pancreatitis and has attended other family reunions. (It was on such an occasion that he visited Jean Burk’s home.) To date, he has studied 746 people from 180 families with hereditary pancreatitis. His research has shown that not everyone with hereditary pancreatitis has the mutation he discovered in 1996. He discovered other mutations of the same trypsin gene that are linked to hereditary pancreatitis. Some of the families in his studies have the first mutation, some of the families have others, but some have no known mutation, so there is at least one other, as yet unknown, mutation that can cause the disease. Whitcomb is now trying to find it.

By studying the inherited disease, Whitcomb uncovered a mechanism important in all forms of pancreatitis.

His discoveries have implications far beyond the 1,000 to 2,000 people in the United States with hereditary pancreatitis. By studying the inherited disease, Whitcomb uncovered a mechanism (trypsin activation) important in all forms of pancreatitis. One percent of the US population is affected by pancreatitis or pancreatic cancer (which is often associated with pancreatitis).

Memorial Day 1996: Whitcomb was back in Kentucky, hosting a second reunion for the family he’d met the year before. He returned to share research results, including his discovery of the gene.

Whitcomb continues to keep the family informed. He publishes a newsletter called *Hereditary Pancreatitis Research News*, which is distributed primarily to participants in his studies. His outreach efforts also include his website devoted to pancreatic disease, http://www.pancreas.org. He receives about four e-mail messages a week from people with pancreatitis who have found his site. *Dear Dr. Whitcomb, read one such message. Hi, the Doctors think I have hereditary pancreatitis because my dad has it too. I don’t really know much about it except that it hurts in your back, sides, and stomach areas (speaking from experience). I’ve been in the hospital for it once because it was the worst attack I’ve had. If you could send me more information on it, it would be greatly appreciated. By the way I’m 12, just in case it matters. . . . Have a nice day.*

Outreach seems to come naturally to Whitcomb, whether the circumstances are professional or personal. Every Wednesday, his family opens up its home to a few dozen young adults from his church.

“They like having a place where they can raid the refrigerator and lay on the floor and play with the dog,” says Whitcomb. They’re also likely to go to him or his wife with personal problems and questions. Some have nowhere else to turn, Whitcomb notes. “It’s fun for us, because they’re all our friends and they’re like our kids. I have a gigantic family.”

An enzyme can inactivate trypsin by cutting the chain that connects the two parts of the trypsin molecule. In some people with hereditary pancreatitis, Whitcomb found, the chain is mutated, and the enzyme is powerless to disable the molecule. (Red arrow above points to chain.) Trypsin has also been implicated in nonhereditary forms of pancreatitis. Yellow star shows active enzyme site.

A few months ago, one of Whitcomb’s collaborators mentioned that he had solved a problem that has puzzled scientists for generations, that is, how the pancreas is able to secrete sodium bicarbonate at the levels that it does. (Sodium bicarbonate is released into the small intestine, where it neutralizes the gastric acid produced by the stomach.) Whitcomb sat down that same afternoon to solve the problem for himself. “I thought, if he’s smart enough to figure it out, I can figure it out,” he says.

Hours later, Whitcomb had the answer. He called his friend back, only to find out there had been a misunderstanding. “Oh, no, that wasn’t the problem we were working on,” his friend said. But Whitcomb believes he has the answer to the ancient mystery, although he is awaiting scientific publication before he explains it to the rest of us.

He stops for a moment to reflect: “There’s a proverb that I like. ‘It is the glory of God to conceal a matter; it is the glory of kings to search out a matter.’ There are things that have been hidden for eons past that nobody’s understood. It is the privilege of kings to have the luxury to investigate what nobody’s been able to figure out. What a job.”