he older man on the other end of the line sounded irritated. He asked Michael Gorin, then an ophthalmology resident at the University of California, Los Angeles, why he had failed to show up at an awards ceremony the previous evening to accept a prestigious honor. Gorin apologized and explained that he hadn’t been notified to attend, then arranged to meet revered ophthalmologist Henry Neburn, the voice on the phone and donor of the LA Ophthalmology Society’s Henry and Lillian Neburn Prize for Research.

When Gorin arrived at the great doctor’s home 16 years ago, the first thing he noticed was the TV: the largest he’d ever seen. It wasn’t that Neburn wanted to watch every close-up during a football game, but that his eyesight had deteriorated to the point where a huge screen was necessary to watch anything. He was basking the advances of macular degeneration. The most common cause of vision loss in people over 60, age-related macular degeneration (AMD) damages the center of the eye’s retina, placing a blind spot in one’s field of vision. Although few people with AMD go blind, many of those affected can no longer engage in daily activities such as reading or driving that require sharp, central eyesight.

What impressed Gorin more than the big-screen TV was Neburn’s ability to lead a full, satisfying life despite his severe visual limitations. So began Gorin’s fascination with AMD and a long friendship. “It’s a good thing nobody shook Henry’s hand at a podium.”

Gorin’s inspiration soon expanded to an exploration of the genetic influences of AMD, shaking Henry’s hand at a podium.”

“Like biology, but discovered that in the lab I drop things,” says Daniel Weeks, looking back on how he ended up as a statistical geneticist. Humility aside, Weeks is clearly no bungler. The 40-year-old chief of Pitt’s Division of Statistical Genetics was singled out this year by the American Public Health Association with the highest honor it bestows on young health statisticians. Weeks makes complex genetic disorders more palpable to researchers at Pitt and throughout the world. His collaborators include Eleanor Feingold, Candace Kammerer, M. Michael Barmada, and Jeff O’Connell. Their forte is making an analysis run smoother and faster as well as reveal more. For example, O’Connell and Weeks made one algorithm run, oh, 7,000 times faster than anyone had before. And almost every paper to come out in the past few years that analyzes family linkages in genetic disorders uses a program that O’Connell wrote to check mistakes that might have been made in labeling genotypes. The division has licensed the program for commercial interests.

The division has licensed the program for commercial interests. “One biotech company with 40 programmers just bought it,” says Weeks. “We have one programmer. That makes me feel pretty good.”
South of San Francisco, off the reef from a town that carries the curious name, Princeton-by-the-Sea, that’s where you’ll find the big wave break: Maverick’s. There, a confined subset of Type As take on 50-degree Fahrenheit water, jagged rocks, shifting currents, and 60-foot-high wave faces funneling into booming tunnels of frothy gray energy. Nature is glorious yet bellicose in these waters. In the past decade, Maverick’s has killed one professional big-wave surfer and injured a few others.

So when Adam Frymoyer, who is new to Northern California and new to catching waves, says, “Have you ever heard of Maverick’s?” it’s fair to wonder—really saying he surfs that break? No, no, and no. Frymoyer doesn’t surf Maverick’s. He is just learning to get up on a board. He is a sensible person. He would, however, like to get a look at those monster waves. But it’s a good idea to check with Frymoyer, MD ’04. It’s not misreading him to take him for someone determined to get the most out of every experience. The 24-year-old Harrisburg native is spending what would have been his third year at the University of Pittsburgh School of Medicine instead as a Doris Duke Clinical Research Fellow at the University of California, San Francisco (UCSF). Fellows receive a $20,000 stipend and a chance to learn the ins and outs of clinical research at one of the Doris Duke Foundation’s six program sites. This is the first year of the program.

Frymoyer landed in San Francisco in July; by September he was finishing up UCSF’s Training in Clinical Research coursework. The program is usually only undertaken by MDs who’ve finished their residencies. (Pitt has a similar program that awards a master’s degree.) He dove right in, soaking up all he could about ethics, execution, and presentation of clinical research. Now he’s pursuing advanced classes in statistics and epidemiology—and anything else he can fit into his schedule. Most of his energy is put toward moving forward clinical trials at various stages of development within UCSF’s Pain Clinical Research Center.

“What sensitization means is this nerve fiber is more reactive, so its threshold to pain is changed,” Frymoyer describes how he creates sensitized pain regions in healthy volunteers. He uses a “heat cap” method, so called because it employs a combination of topical capsaicin and heat. The idea is to mimic the experiences of chronic pain sufferers. Frymoyer’s enthusiasm for the project makes one consider signing up, even though the intended end for the trial volunteer is straightforward: Pain. For a little while anyway.

He is able—temporarily and gently, at the level of a first-degree burn—to get a nervous system to respond in much the same way it would complicate the life of someone suffering from, say, postherpetic neuralgia (the pain some people continue to experience years after a shingles attack). One of the phenomena he’s able to mimic is known as allodynia—which can make a seemingly harmless stimulus, like the grazing of a shirt, actually hurt. He softly takes a brush to an arm to demonstrate: “If I rub with this brush, it just feels like a brush, right? It’s not painful. After this heat cap model, if I rubbed you then, it would become painful, unpleasant.”

His UCSF mentors, Michael Rowbotham and Karin Petersen, developed the model as a way to determine the effectiveness of new analgesics before proceeding to more costly and complicated trials. Using the model, Frymoyer is testing a compound for a pharmaceutical company. He’s helping with other trials as well.

This isn’t Frymoyer’s first immersion in research. He spent the summer of 2000 as a fellow of the American Pediatrics Society—a good experience. Still that was only eight weeks. “I wanted to fit clinical research into my future,” says Frymoyer. “I wanted to have the proper background and training. Something to go on.” At the end of his second year in med school, he told himself it was now or never. He wanted to do a year of research without interrupting his third and fourth year rotations.

Now he is seeing the life of a clinical researcher up close. Rowbotham, who happens to be an avid surfer, takes him on rounds. (He also has offered to take him to some nice breaks. Frymoyer wants to make sure he can stay up on the board for a while before he puts himself on the spot with his boss, though.)

This fellowship has been exactly what he hoped for, and more. Frymoyer doesn’t even mind all the paperwork for internal review boards and state advisory panels. That’s part of protecting human subjects, he’ll say. He just wants to make sure he knows exactly what to expect when he’s an MD running trials himself.
CLUES TO CHILD ABUSE

When Kochanek began studying the samples, he set out to understand better, at the molecular and biochemical levels, how a brain is injured by trauma. He explains that there are two phases of injury. There’s primary injury—which destroys a certain number of neurons. But the majority of brain damage occurs from secondary injury—neuron damage in the region surrounding the site of the impact, which takes place in the hours and days following the impact. Kochanek focused on mechanisms of secondary injury.

In so doing, he discovered that child abuse victims stood out as a very distinct subpopulation within his group of severe head trauma victims. Their glutamate levels, for example, were off the chart. Glutamate is an excitatory neurotransmitter, essential to cognition in a healthy brain. The victims of accidents had elevated glutamate levels. Known victims of child abuse—who suffered head trauma from being shaken, from having their head hit against a wall or other object, or from blows to the head—had glutamate levels that were several times higher than levels in accident victims. A high level of glutamate in the brain, in combination with the low blood flow that results from the high intracranial pressure, creates seizure-like conditions. Kochanek believes this condition is one mechanism for secondary injury of brain tissue.

Collaborator Robert B. Clark, of the anesthesiology department, came across another biological tattler. Cytochrome C is a protein found in the mitochondria and plays an important role in normal cell function. When released into the cytoplasm, however, it triggers cell death. Clark tested CSF for cytochrome C and found it in only two subpopulations of severe head trauma victims—those who died and child abuse victims. This suggests that the brains of child abuse victims are more severely injured than those of accident victims, and that they are injured in a qualitatively different way. The differences could be caused by many factors, including the multiple injuries abused children often suffer and the delay in treatment typical among victims of abuse.