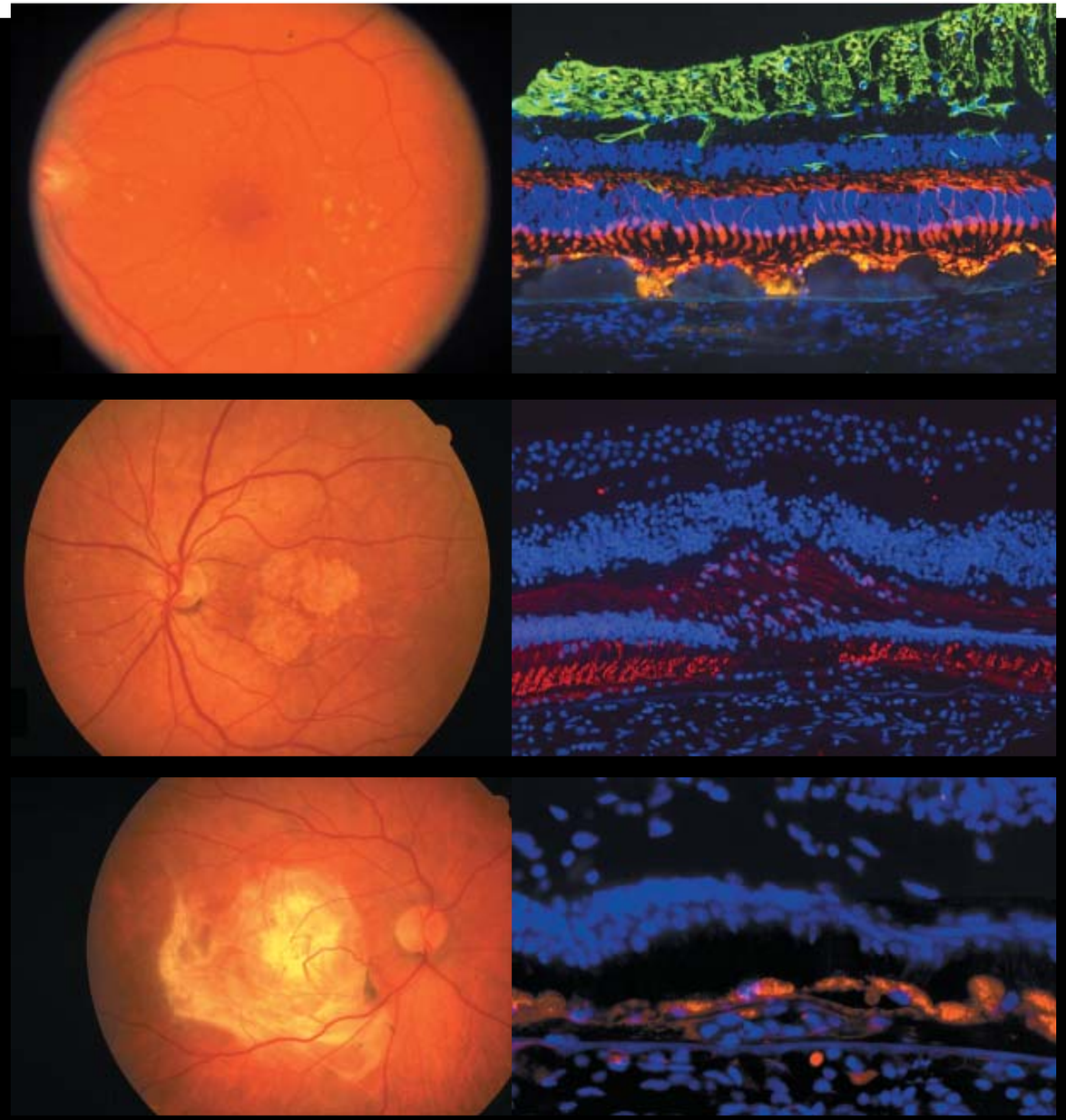


TOP LEFT: Yellow spots in the eye are drusen, deposits found in many people with early age-related macular degeneration (AMD). TOP RIGHT: Detailed view of drusen. MIDDLE LEFT: Eye with "dry" AMD, the more common and less severe form of the disease. The yellow areas are blind spots caused when the pigment epithelial cells underneath the retina atrophy. MIDDLE RIGHT: Detailed view of the atrophied cells. BOTTOM LEFT: Eye with "wet" AMD, the more severe form of the disease. Yellow area is a blind spot caused by abnormally growing blood vessels that leak, triggering scarring. BOTTOM RIGHT: Detailed view of scarring. Sixty-five percent of the patients in the Pitt study had "wet" AMD; the rest had "dry" AMD.

DR. ANN H. MILAM, SCHEIE EYE INSTITUTE, UNIVERSITY OF PENNSYLVANIA

FOUND: MACULAR DEGENERATION GENES

LOST: THE EARLY AND LATE-STAGE DISEASE LINK | BY TRINA WOOD

The 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 Nesburn, the voice on the phone and donor of the LA Ophthalmology Society's Henry and Lillian Nesburn 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 Nesburn wanted to catch 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 battling 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 Nesburn'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 ever told me about attending that evening," says Gorin, who is now interim chair of ophthalmology at the School of Medicine. "It's unlikely I'd have been inspired as I was just shaking Henry's hand at a podium."

Gorin's inspiration soon expanded to an exploration of the genetic influences of AMD, which afflicts more than 13 million Americans.

After more than a decade of compiling genetic data on 860 people from nearly 400 different families, Gorin and his colleagues, including Daniel Weeks, associate professor of human genetics, have now identified loci, or regions, on four separate chromosomes that appear to contribute to AMD susceptibility. The study, which appeared in the November 5 issue of the *American Journal of Ophthalmology,* suggests that regions on chromosomes 1 and 17 are most strongly linked to AMD; chromosomes 2 and 12 also appear to be somewhat involved.

Working with a late-onset disease presents a big challenge because genetic information from the parents of elderly patients is often unavailable. In hundreds of the cases in the AMD study, no blood samples existed from parents. So Weeks (who is the lead author on the November paper) had to determine their probable genotypes on the basis of offspring genotypes. Their study also took some wind out of a long-held hypothesis: that is, the same genes that contribute to juvenile macular dystrophies must also be major contributors to AMD. They probably aren't after all, says Gorin:

"We used to think that early onset disease and late-onset disease would simply reflect different variations in the same genes. However, our study suggests that this is only true for a very limited set of cases, and it is likely that different genes contribute to different forms of a disease." (These findings mirror studies by researchers comparing early and late-stage onset forms of complex genetic disorders such as Parkinson's and glaucoma, Gorin notes.)

Gorin is now interested in looking at additional families to verify their data and identify more precisely the genes involved in AMD. With that knowledge in hand, researchers could use genetic testing to identify high-risk individuals when they are asymptomatic. They would also be able to study how genes are regulated in order to develop therapies that might slow the progression of the disease. And that, in the long term, would mean ophthalmologists could test therapies to see if the risk of vision loss can be minimized.

In the next five to 10 years, Gorin hopes to collect enough data to conduct an interventional clinical trial with people known to be at high risk for AMD. "That's where genetic testing is of real value—in the preventive approach," he says. ■

DO THE NUMBERS

"I 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 note they wouldn't even consider taking on huge, dense studies—such as pinpointing the genes responsible for age-related macular degeneration—without knowing they'll have guidance from the likes of Weeks and colleagues. His division's core faculty members 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. "One biotech company with 40 programmers just bought it," says Weeks. "We have one programmer. That makes me feel pretty good." *—EL*



Frymoyer

ERICA LLOYD

UP CLOSE

AMONG THE FIRST DORIS DUKE CLINICAL RESEARCH FELLOWS | BY ERICA LLOYD

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 belligerent 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—*he's not really saying he surfs that break?*

No, no, 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.

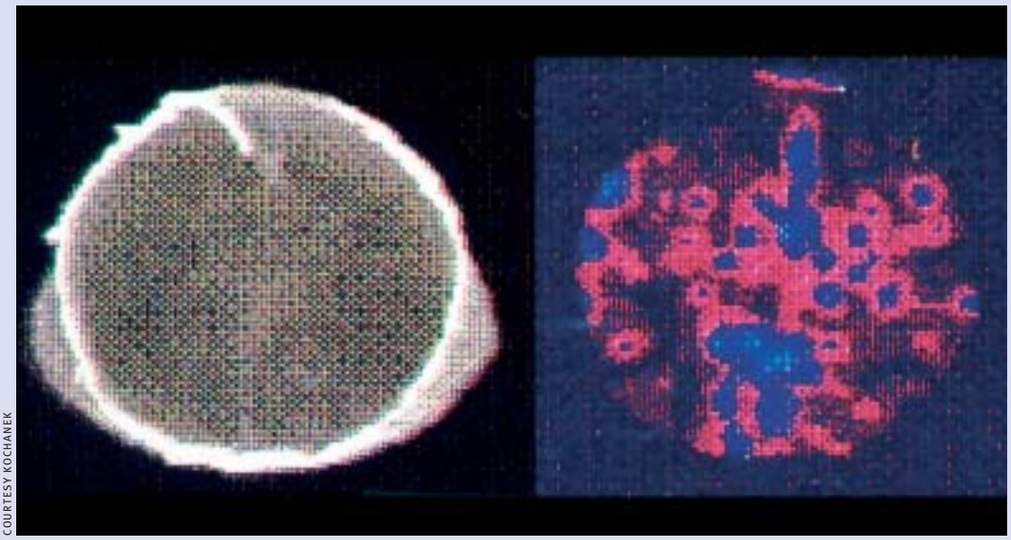
Now he is seeing the life of a clinical researcher up close. Rowbotham, who happens to be an avid surfer, takes him on rounds. (He also has offered to take him to some nice breaks. Frymoyer wants to make sure he can stay up on the board for a while before he puts himself on the spot with his boss, though.)

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

BRAIN DAMAGE THAT'S BIOLOGICALLY DISTINCTIVE

BY JENNIFER LEE AND DOTTIE HORN



COURTESY KOCHANEK

This cerebral blood flow map is from a month-old infant who has suffered severe head trauma as a result of child abuse. The map shows that the infant has very low blood flow to the brain. The inadequate blood flow increases the brain's susceptibility to damage.

Sometimes, brain damage hides. It's not unusual for pediatricians in their clinics to examine children who "just don't look right." Maybe a toddler is irritable, colicky, or her color is off—that can mean cerebral damage, but there's no clear evidence. In such cases, it can be difficult to justify a CT scan, which is often revealing. The work of Pitt MDs Patrick Kochanek and Rachel Berger is likely to help such diagnoses. Berger is one of several faculty and fellows working with Kochanek to give the medical community an understanding of the damaged brain at a new level. Kochanek, a professor of anesthesiology, critical care medicine, and pediatrics, is hopeful these studies will lead to, among other advances, a blood test that can pick up biological markers of damage. The work may even offer new ways for physicians to identify cases of abuse.

This is an outcome Kochanek wouldn't have predicted. "The child abuse angle came out of the woodwork," he says.

If a child suffers from severe head trauma, from a car accident, for example, the brain tissue swells, and pressure builds inside the skull. As the pressure grows, it becomes harder and harder for blood to flow through the vessels in the brain. Hours later, the child is likely to be comatose and on a respirator. Neurosurgeons like Kochanek's colleague David Adelson may drain cerebrospinal fluid (CSF) in order to relieve some intracranial pressure. CSF is a clear fluid that continuously percolates around the brain.

In most cases when CSF is drained, the fluid is thrown away. But, seven years ago, Kochanek decided to begin collecting and studying CSF from pediatric cases. Other researchers had studied the fluid, but Kochanek wanted to submit it to a more extensive battery of tests. Few had studied CSF from children. Kochanek began collecting samples and, soon after, initiated a pediatric CSF bank, which is now funded by the Centers for Disease Control and Prevention.

In a freezer housed in the Safar Center for Resuscitation Research, which Kochanek directs, sits a collection of about 1,000 samples of CSF gathered from about 100 infants and other children. In most cases, samples were taken sequentially from patients, to allow scientists to study changes over time.

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—the impact itself—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. ■