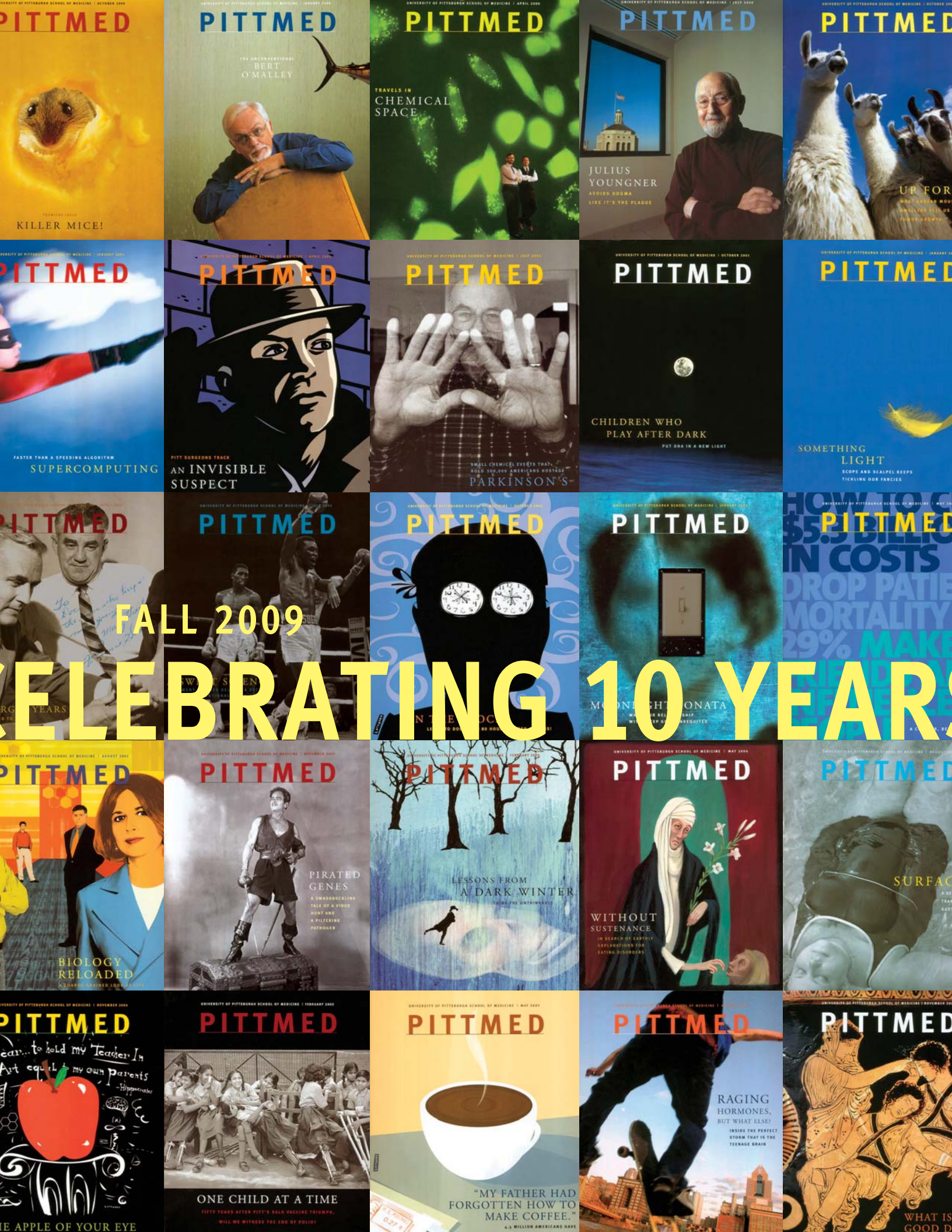

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WHAT IS GOOD P

STOLZOSCOPY

I am a School of Medicine alum (PhD '02), and I teach biology at the fourth largest private institution of higher learning in Texas, the University of the Incarnate Word. Several of our classes involve teaching our students the concept of electron microscopy and how it has opened up a whole new world for us to visualize and appreciate.

I was very impressed by the work of Dr. Donna Stolz and her associates at the Center for Biologic Imaging who collated all of those wonderful TEM (transmission electron microscopy) and SEM (scanning electron microscopy) images into the format of a Periodic Table ["What Would Mendeleev Do?" Spring 2009]. The time and effort it must have taken to find all of these images and present them in this format! Dr. Stolz has given educators a wonderful teaching tool. Several faculty members in my department plan to incorporate the table into their course material.

Again, I would like to congratulate Dr. Stolz, the Center for Biologic Imaging, and the persons responsible for choosing this work to be published in *Pitt Med*.

Ana C. Vallor, PhD
San Antonio, Texas

We gladly receive letters (which we may edit for length, style, and clarity).

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Carnegie Science Center Journalism Award
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Gold, Periodical Staff Writing

CASE District II Accolades
Gold, Best Article
(J. Miksch, "The Investigator's Path")

CASE District II Accolades
Silver, Covers (Summer 2008)

IABC Golden Triangle Award of Honor
Magazines

IABC Golden Triangle Award of Honor
Magazine Design (E. Cerri)

IABC Golden Triangle Award of Honor
Feature Writing
(E. Vitone, "What Possessed You?")

Pittsburgh Black Media Federation
Robert L. Vann Media Award,
Magazine Features, Third Place
(C. Zinchini, "Twins")

CORRECTIONS

In our Summer 2009 issue, we noted the election of Pitt's Michael Fine (Res '87) and Mark Gladwin to the Association of American Physicians. Fine is an MD professor of medicine and Gladwin is an MD professor of medicine and chief of the Division of Pulmonary, Allergy, and Critical Care Medicine. We accidentally omitted the election of Merrill Egorin, MD professor of medicine and of pharmacology and chemical biology (noted in this issue); David Rothstein, MD professor of surgery, medicine, and immunology; and Gary Silverman, MD/PhD professor of pediatrics and chief of the Division of Neonatology and Developmental Biology.

THURSDAY NIGHT LULLS

The end of NBC's *ER* meant the end of an era for some. Two Pitt med-ers—an alumnus and a student—share how a TV show taught them important lessons about becoming physicians. You can find these "Web-extra" essays by Ram Gordon (MD '98) and Sarah Ramer (Class of 2011) at ...



ttp://pittmed.health.pitt.edu

Two episodes you won't want to miss.

PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, FALL 2009 (AUG/SEPT/OCT)

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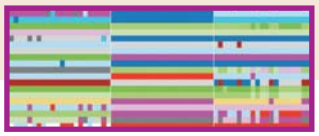
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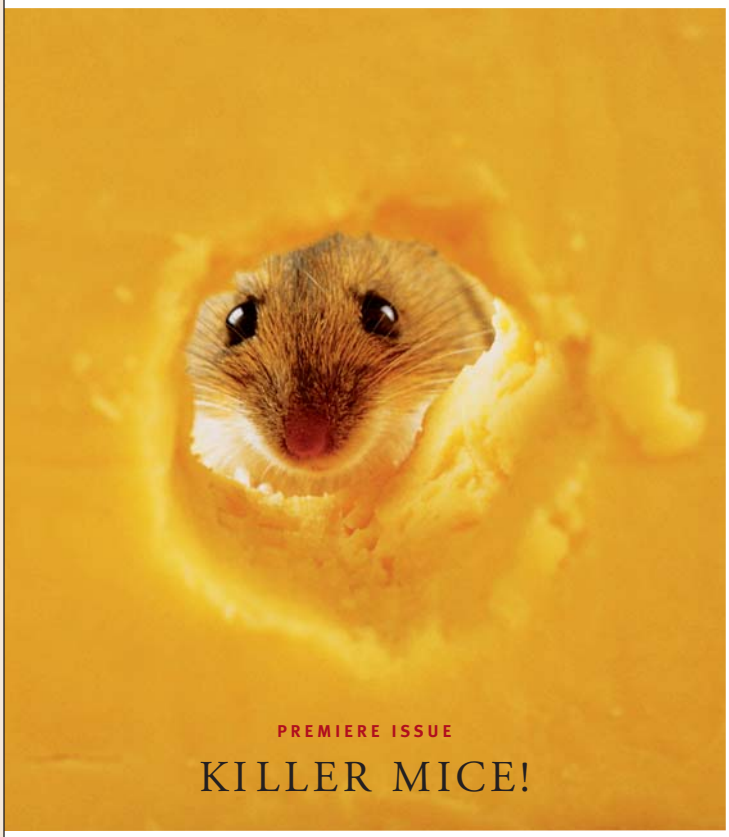


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PREMIERE ISSUE

KILLER MICE!

COVER STORY

10 for 10 12

Happy birthday to us! Ten years ago, we published the first issue of *Pitt Med*. This, the one you're reading now, is our 40th. In the course of that decade, University of Pittsburgh School of Medicine people have found that presumed molecular enemies can also be our friends; that it's not only possible, but it can be advisable, to remove brain tumors through the nose; that a medical school can mold graduates who are primed to be physicians *and* scientists; and then some.

We've done our best to keep up. And now we go back to some of those compelling stories—even with 20 pages' worth, not nearly enough space to do the school justice—to see how things have progressed. Delve in with us and see what a difference a decade can make.

BY BRANDON ELLIS, REID R. FRAZIER, ERICA LLOYD, JOE MIKSCH, CHUCK STARESINIC, SHARON TREGASKIS, ELAINE VITONE, AND MELINDA WENNER

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18. "Lessons from a Dark Winter," illustration by David Pohl.
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29. "Evolution of Flu," image by Elodie Ghedin/ Nature Publishing Group.
30. "Built to Last," image by Tallini, Y.N., et al., National Academy of Sciences, USA. *(Covers 30 and 31 out of chronological order.)*
31. "What Possessed You?" illustration by Catherine Lazure.
32. "'Plain People,' Complex Cures," photo by Cami Mesa.
33. "Meet Steven Shapiro," photo by moodboard/Corbis.
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36. "Reply at Your Own Risk," typography by Elena G. Cerri.
37. "Breathless," photo by Steph Hooton/Pictogram Studio.
38. "In a Sea of DNA," image by Bennett Van Houten.
39. "Caring for Kids," photo by Esther Bubley/ Children's Hospital of Pittsburgh of UPMC.
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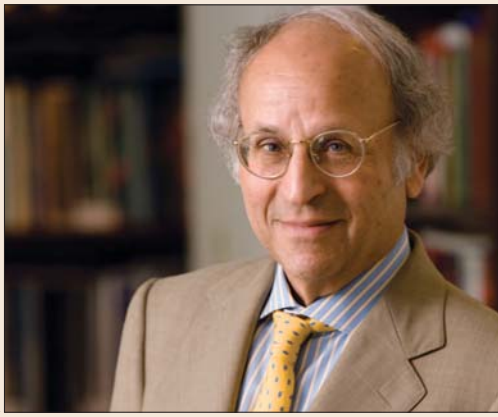
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JOSHUA FRANZOS

In the long history of humankind (and animal kind, too), those who learned to collaborate and improvise most effectively have prevailed.

— Attributed to Charles Darwin

In the previous issue of *Pitt Med*, we described the research of Cecilia Lo, the founding chair of our new Department of Developmental Biology. We noted that in 2007, she identified a gene in mice, homologous to a human gene, that when mutated causes a complex congenital heart disease known as "heterotaxy," in which a severely abnormal heart is on the right instead of the left. The mutation also results in a defect in the function of the cilia that line the respiratory tract (primary ciliary dyskinesia). This was the first evidence that the heart disease is genetically linked to this dysfunction in cilia.

As it turns out, virtually all of our cells have cilia—hairlike "antennae" that protrude from the cell surface, with some moving like a wave and others remaining stationary; and these structures are highly conserved in evolution. (You may remember meeting the cilia's lengthier ancestor, the flagellum of the single cell *paramecium,* in high school biology.) Dr. Lo and others suggest that at the earliest stages of embryonic development, the orchestrated waving of the cilia on primitive heart cells affects the patterning of the cardiovascular system, possibly by making the cells "swim" from right to left in the embryonic fluid (in typically developing embryos). Non-motile, single cilia detect light, odor, fluid flow, mechanical stress, and sound. They act as a signaling machine, communicating indirectly with our genes and transporting proteins in both directions between the cilium and the cell body, thereby influencing the regulation of critical cellular processes such as cell division, cell differentiation, and wound healing—as well as embryonic development. Motile cilia dysfunction may lead not only to respiratory and cardiac disease, but to male infertility, cystic kidney disease, or hydrocephalus. In some circumstances, both types of cilia might work together; for example, motile cilia on kidney tubule cells could influence fluid flow and stationary cilia could sense that flow.

Cilia allow the *paramecium* to move toward food, and later in evolution, they bring the sperm toward the egg, shape us, and organize our brains. It strikes me that the activity of cilia is a fine metaphor for human behavior. We often stay still, sensing our environment and reacting accordingly—sometimes joining others as we move together in response to what we have sensed. But our collective behavior isn't always coordinated or constructive. I think of this metaphor now as I view the ongoing debate over health care reform. Most of us agree that every American should have health insurance and decent care of good quality at a cost that will not bankrupt us individually nor as a country. Yet, as I write this, powerful institutions and Congress have not yet fully sensed the needs of all of our people, nor moved collectively and constructively to address those needs.

In the end, an appropriate strategy for reform will hopefully be selected—by legislation if not by nature—only several decades after Harry Truman recognized the imperative to do so. But then again, evolution moves slowly. *Paramecium* to person didn't happen overnight.

Arthur S. Levine, MD
Senior Vice Chancellor for the Health Sciences
Dean, School of Medicine



Devoted to noteworthy happenings

at the medical school

LUNA TO ADVISE NIH DIRECTOR

Beatriz Luna, a PhD and professor in the Department of Psychiatry who studies the adolescent brain, has been appointed to the Advisory Committee to the Director of the National Institutes of Health. She is the first University of Pittsburgh School of Medicine faculty member to serve in this capacity. Luna will assist in developing policy regarding such issues as the grant application process and conflict of interest.

"They [at the NIH] really want to hear your opinion," Luna says. "Most other members are more senior and more administrative. I think I represent the person in the trenches."

—Joe Miksch



Luna

FOOTNOTE

Alan Russell is six places ahead of Will Ferrell and can see President Barack Obama's back. *Rolling Stone* ranked Russell—a PhD University Professor of Surgery and director of the Pitt-UPMC McGowan Institute for Regenerative Medicine—32nd on its list of "The 100 People Who Are Changing America." Calling him "a medical futurist who is finding ways for the body to rebuild itself," the magazine notes that Russell and others are developing an artificial ovary for women whose ability to have children has been compromised by cancer.

HELLO, MR. PRESIDENT

Gonzalo Torres is the third University of Pittsburgh School of Medicine faculty member to win a Presidential Early Career Award for Scientists and Engineers. He and 99 other PECASE winners will be honored at a White House ceremony noting their achievements. Torres is one of 12 nominated by the National Institutes of Health for the prize.

Torres, a PhD assistant professor of neurobiology, researches the regulation of dopamine in the brain. His efforts to understand the molecular mechanisms of this process, which Torres says turns out to be more complexly organized than anticipated, have implications for the treatment of schizophrenia, Parkinson's, and drug addiction.

"I have to emphasize that this is the work of a group of people," Torres says. "This is a team effort that is being recognized."

The honor, first given in 1996, carries with it up to a five-year grant and represents the highest honor bestowed upon young scientists and engineers by the federal government. J. Peter Rubin, of Pitt's Department of Surgery, won in 2006, and Karl Kandler, of the departments of otolaryngology and neurobiology, in 2000. *–JM*



CAMI MESA

A&Q

David Kupfer: Writing *DSM-V*

It's a job that carries a measure of prestige and is an awful lot of work. Since 2006, David Kupfer has served as chair of the task force charged with revising the venerable *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), the bible of psychiatry. The process involves hundreds of experts, reams of research, and some politics.

Kupfer, an MD and the Thomas Detre Professor and chair of the Department of Psychiatry at the University of Pittsburgh School of Medicine, as well as director of research at Western Psychiatric Institute and Clinic of UPMC, says the new edition ought to be ready for publication in 2011, 17 years after the *DSM-IV* was released. Kupfer talks about the weight of making the *DSM-V* a reality.

On managing outside pressure

There are a variety of influences—ones that have to do with commercial interests and could be represented by pharmacology companies, insurance companies, device makers—but they may also be represented by advocacy groups for certain kinds of disorders.

We've gone out of our way to have a higher standard of transparency and insist that [task force and work group members] are free of any undue involvement with commercial interests. All members are limited to $10,000 in annual income from *all* commercial interests.

On changes in the field

The use of imaging [fMRI, CT scans, etc.] has become more prominent in psychiatry. I don't know how much of this work will pass muster for this edition, how much is ready for prime time. We're also thinking about disorders as having a continuum. Under the current criteria, once you turn 18, you can no longer have ADD (attention deficit disorder), and we know that's not truly the case.

On changes to the *DSM* itself

The *DSM* is revised once every 20 years or so. We're setting up a [computer-based] system that will allow findings that might hit a threshold of replicability to be put into the *DSM* between revisions. This won't happen often, but we want to make it a living document.

His question for us

What kind of feedback would you give to help us make the *DSM* more friendly and useful to clinicians and their patients? *Send responses to medmag@pitt.edu* —*Interview by Joe Miksch*

Faculty Snapshots

Gwendolyn Sowa is the Association of Academic Physiatrists' 2009 Young Academician. The MD/PhD assistant professor of physical medicine and rehabilitation studies spine degeneration and the mechanisms of back pain at the molecular level.

She hopes to find a biomarker that can tell doctors when exercise is facilitating physical repair of back injuries.



Sowa

Merrill Egorin received the 2009 American Society of Clinical Oncology Translational Research Professorship for his efforts to improve cancer treatments and his support for the next generation of researchers. Egorin is an MD professor of medicine and of pharmacology and chemical biology and a member of the University of Pittsburgh Cancer Institute. He is also one of five Pitt faculty members who recently joined the august ranks of the Association of American Physicians, which honors investigators who convert basic science into clinical practice.



Egorin

With colleagues in the Division of General Academic Pediatrics at Children's Hospital of Pittsburgh of UPMC, Alejandro Hoberman finds ways to help doctors become better at what they do. Hoberman is chief of the division, and he and his faculty set a goal eight years ago to build on their strong clinical and research foundations to create an exceptional teaching program with particular emphasis on developing tools for physicians of all experience levels. The Academic Pediatric Association thinks they've been doing an excellent job; the organization bestowed its 2009 Outstanding Teaching Award on the division. Hoberman, an MD professor of pediatrics in the School of Medicine and Jack L. Paradise Professor of Pediatric Research, says that the program has thrived because of faculty investment in curriculum development and inspiration from early mentors. Of particular note, Hoberman says, is ePROM (enhancing Proficiency in Otitis Media), which is sponsored by the Centers for Disease Control and Prevention and is used in pediatric hospitals throughout the world. —*JM*



Hoberman

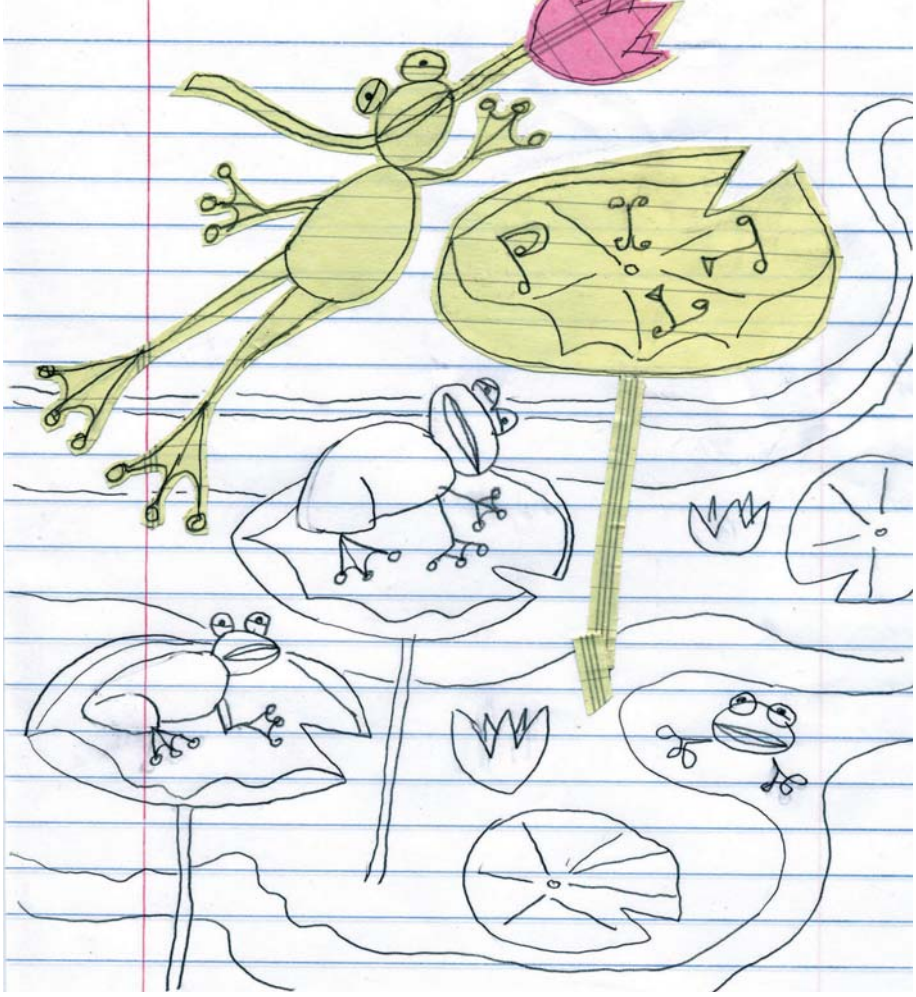
Movin' on Up

The preliminary fiscal year 2008 numbers are in, and the University of Pittsburgh and its affiliates appear to have ascended to fifth in National Institutes of Health funding.

Arthur S. Levine, senior vice chancellor for the health sciences and dean of the School of Medicine, suggests that the approximately $440,761,000 in grants is a reflection of the University taking the right tack when it comes to prioritizing research.

"We've built a lot of basic science [space] over the last decade," he says. "We've made good decisions when it comes to recruiting the right people to fill that space, and we've paid attention to the types of research we've chosen to pursue."

Levine also considers the high ranking an indication of the overall quality of the School of Medicine. "If you're ranked that high, you must be a sophisticated, intelligent, and creative institution and therefore attract good students, good teachers, and provide good patient care." *—JM*



CATHERINE LAZURE



SCIENCE PHOTO RESEARCHERS

Less Pain, More Gain

A new bone marrow transplant regimen, initiated by Lakshmanan Krishnamurti at the University of Pittsburgh, has the potential to make the cure for sickle cell anemia a much easier road to travel.

Most sickle cell patients don't live past their 40s. The hereditary disorder—in which red blood cells are misshapen (see above) and can clump in blood vessels, leading to pain, organ damage, high blood pressure, and stroke—affects 70,000 in the United States, most of whom are African American.

Bone marrow transplantation, which results in the generation of new, healthy red blood cells, has been used to cure the disease since the early 1980s. However, the radiation and chemotherapy used to prep patients for transplant make the procedure an unattractive option to many.

Krishnamurti, a Pitt MD associate professor of pediatrics and director of the Comprehensive Hemoglobinopathy Program at Children's Hospital of Pittsburgh of UPMC, has found that reducing doses of radiation and chemo makes the process more tolerable for patients—and equally, if not more, effective.

In a recent clinical trial, all seven patients were cured of sickle cell. Krishnamurti also found that because the patients' bone marrow was not obliterated by high doses of chemo and radiation, their own white blood cells mingled with those of the donors, giving them an advantage in fighting infection. *—JM*

MEN RESPOND DIFFERENTLY TO INFECTION

Women live five to seven years longer than men. After examining how men and women respond to infection, the University of Pittsburgh's Derek Angus has found another factor that might help explain the disparity.

Angus, an MD/MPH who is chair of Pitt's Department of Critical Care Medicine, and his team collaborated with 28 hospitals nationwide to monitor 2,320 patients with pneumonia. Twenty-one percent of men died within one year after hospitalization compared to 16 percent of women, a difference not explained by demographics, chronic health conditions, health behavior, or quality of care. Men responded to infection with higher levels of inflammatory and coagulatory molecules in their blood, which may have contributed to sepsis and death.

The study is one of the largest to examine sex differences in infection response and hints at a future where gender may influence how infection gets treated, says Sachin Yende, an MD assistant professor of critical care medicine and corresponding author of the study, published in the May issue of *Critical Care Medicine*. *—Brandon Ellis*



FRANK HARRIS

PITTSBURGH TO KENYA, BY FOOT

It's 7,000 miles from Pittsburgh to Kenya, but Pitt med students have done an admirable job of bridging the gap.

In 2002, a group of Pitt med students spent several weeks working on a malaria research project in Kenya, where they encountered children and families devastated by HIV/AIDS. Individuals and informal community groups with little outside support helped these children. Back in Pittsburgh, the students created the Kenya Pediatric HIV Project (KPHP) and have since raised more than $40,000 for the cause.

Jackie Ryan (Class of 2010) conducted research for her scholarly project in Kenya in 2007. There, she got to know a woman running an orphanage outside of the small town of Kilifi. The woman and her husband had children of their own but had somehow become the caretakers of boys and girls whose parents had died of AIDS. Some two-dozen of these children slept together on the floor of a one-room building that was also their school. With Ryan's help and a donation from KPHP, this spontaneous orphanage was able to purchase bunk beds, bedding, school uniforms, and shoes.

The fundraising continues. On April 4, KPHP held its annual 10K and 5K race in Pittsburgh's South Park. By partnering with Pitt's Student Leaders in International Medicine, KPHP made this year's event the biggest ever, attracting 600 runners and raising more than $5,000 for Kenyan children. *—Chuck Staresinic*

Appointments

Rocky Tuan envisions a day in which cell biology and engineering merge and allow doctors to help patients regenerate cartilage, tendons, ligaments, peripheral nerves, and bone.

Getting to that point merely requires a complete understanding of the body's innate healing process, the molecular signals that tell cells what to do, the workings of cellular growth factors, and on and on and on, he says with a laugh.



Tuan



Kensler

Tuan will attempt to take medicine further toward his vision as founding director of the University of Pittsburgh School of Medicine's Center for Cellular and Molecular Engineering and as a professor of orthopaedic surgery. The PhD investigator comes to Pitt from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, where he served as chief of the cartilage biology and orthopaedics branch.

"I want to create a forum where all in the University community who think along these paths can collaborate to restore function to damaged and injured tissue," he says. Tuan is the husband of Cecilia Lo, who came to the school this summer to serve as the founding chair of the Department of Developmental Biology. (See our Summer 2009 issue for more on her appointment.)

Thomas Kensler will join the School of Medicine faculty this winter as a professor of pharmacology and chemical biology. Formerly of Johns Hopkins University Bloomberg School of Public Health, Kensler will continue to pursue research into the biochemical and molecular mechanisms of cancer.

Of particular interest to Kensler, a PhD, is a rare liver cancer caused by aflatoxin, a fungus-produced carcinogen that acts in concert with hepatitis B virus. In his research, Kensler has found signaling pathways that, when activated, seem to enhance resistance to aflatoxin and other environmental carcinogens and are targets for preventative therapies.

Kensler will hold a joint appointment in environmental and occupational health in Pitt's Graduate School of Public Health. He is married to Nancy Davidson, newly appointed director of the University of Pittsburgh Cancer Institute (whom we wrote about in our Spring 2009 issue). *—JM*



NOURISHED IN HAITI

In Haiti's central plateau, unemployment hovers around 80 percent. The island nation has been almost deforested by people seeking fuel for cooking. Food can be scarce.

After completing his undergraduate degree at Oxford University, Dipesh Patel took classes at the University of Miami. While there, he raised money for and volunteered in a mission to Ecuador. Among the sources of funding his group relied on were the Rotary Clubs of South Florida. By 2005, Patel was looking for a project that, to succeed, counted on the involvement of those being served rather than simply serving them. He started talking to a friend about Haiti. Then a former Haitian health minister shared an idea with Patel.

Today, Patel is a third-year student in the University of Pittsburgh School of Medicine. And finally, he has seen the minister's idea come to fruition. Haiti's central plateau residents will soon have a fully functioning, potentially lifesaving, factory that produces Akamil, a staple food consisting of cereal, beans, minerals, and vitamins.

"It was an incredible idea built on sustainability and empowerment," says Patel. "Unfortunately, nutrition isn't quite the 'sexy topic' in medicine or public health and is often ignored. This ... is exactly what attracted me to the idea."

Patel is cochair of a nine-member group that raised $112,000, primarily from the Rotarians, for the project, which is overseen by Project MediShare, a nonprofit organization started by University of Miami physicians. The factory will open this fall and can produce up to 10 tons of Akamil daily. A pound of it costs 40 cents and can feed a family of three for a day, Patel says.

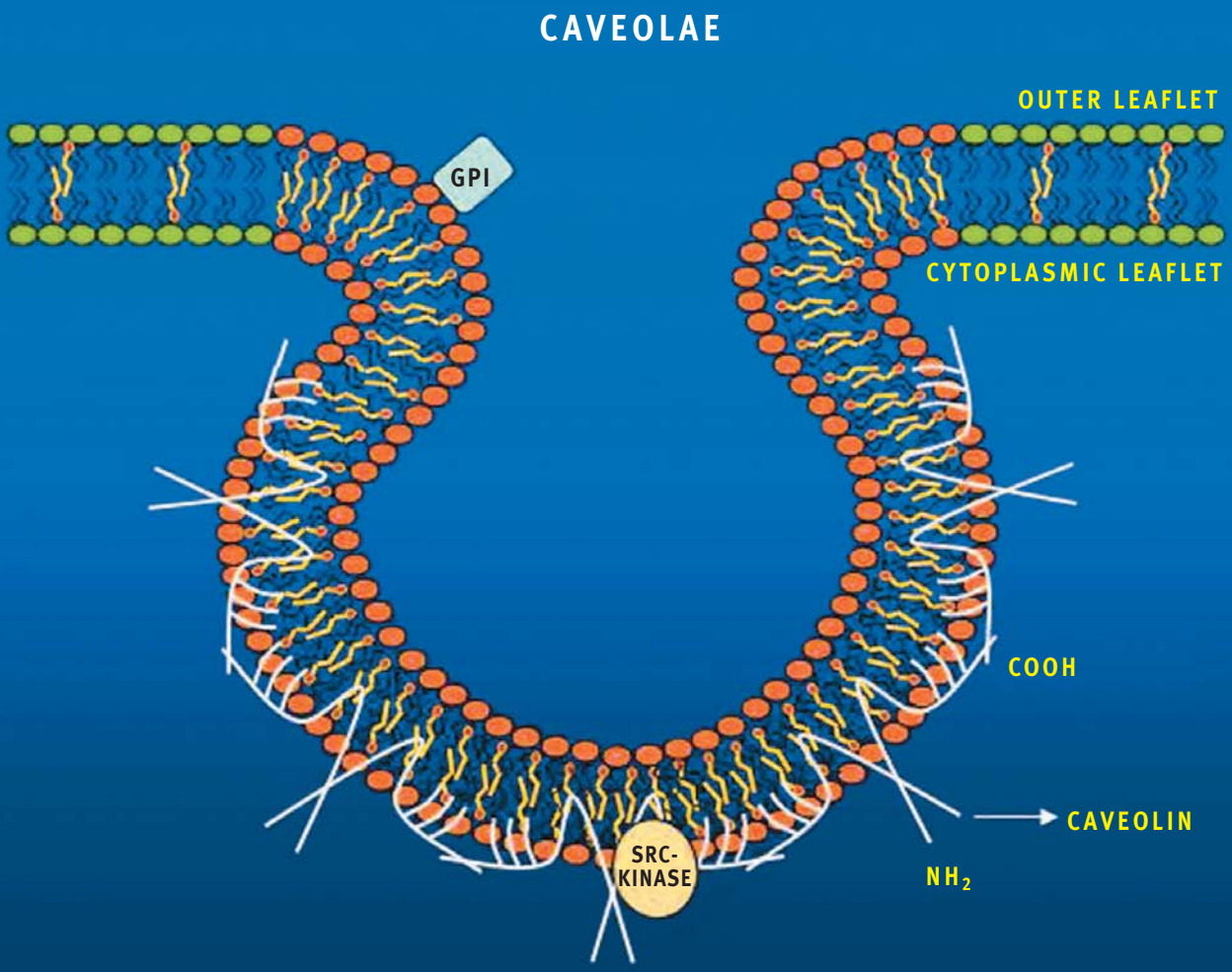
The cereal and beans are grown by local farmers. The Akamil will be sold by women's cooperatives, who are given start-up capital in the form of microcredit loans. The project also involves a training component for farmers and salespeople, housing, and teaching uses for Akamil and the value of healthy eating.

In between his Pitt classes, rotations, and research on pneumonia in children younger than 5 (the biggest killer of young children worldwide), Patel volunteers at local clinics and shelters and for the homeless. He plans to maintain a high level of community involvement in whatever medical specialty he chooses for his career.

He'll go back to Haiti for the opening.

"It's self-sustaining," Patel says of the Akamil project.

"We thought it would take six months, but it's taken three years. We think it will make a difference." *—Joe Miksch*



When the protein caveolin-1 is expressed the cell membrane creates caveolae, or "little caves." Through these caveolae, cells execute signaling and transduction. An increase in caveolin-1, Pitt researchers have found, contributes to the development of certain diseases, like emphysema, while reducing the risk of others, including some types of cancer.

SMOKED CELLS

EMPHYSEMA LINKED TO PREMATURELY AGING CELLS | BY REID R. FRAZIER

Imagine for a moment that you are a lung cell. You work for a smoker. (Okay, so life's not fair sometimes.) Specifically, you're an epithelial cell in the alveoli, the grapelike sacs at the lung's outer reaches, where blood trades gases with inhaled air—carbon dioxide for oxygen. (Hey, at least you have an important job.)

Then your host lights up. (You've tried to get him to quit, but that's another story.) Smoke, filled with all kinds of ne'er-do-wells called free radicals, surrounds you. You don't feel so good now—scientists haven't quite narrowed down which of the many miscreants in the smoke are so bothersome, maybe all of them—and you instinctively call for help. The body's inflammatory system arrives to help, but it does more harm than good, and somewhere along the line, you stop working so well. This isn't so good for you. In fact, you and your host could die because of this response.

This is roughly what happens in emphysema, a key component, along with chronic bronchitis, of chronic obstructive pulmonary disease. Ninety percent of COPD patients smoke or have smoked. It is a smoker's ailment.

And it is the country's fourth leading cause of death, affecting perhaps 24 million Americans. By 2020, COPD is projected to be the third leading cause of death on the planet.

Yet relatively little has changed in COPD therapies in the past generation.

"We haven't had anything that's improved patient outcomes since oxygen [inhalation] was introduced in 1980," says Steven Shapiro, Jack D. Myers Professor, chair of medicine, and a pulmonary critical care specialist at the University of Pittsburgh. Oxygen therapy helps patients with low levels of blood oxygen, but, Shapiro says, "It's not rocket science."

Pitt researchers have discovered a cellular pathway that could lead to new COPD therapies in the future. They've shown that high levels of a protein called caveolin-1 play a role in triggering smoking-related emphysema, mainly by prematurely "aging" lung cells through a mechanism called cellular senescence. The frontman for this research is Pitt's Ferruccio Galbiati, of the Department of Pharmacology and Chemical Biology. For the past 15 years or so, Galbiati, a Milan-born PhD, has been studying caveolins, the structural protein—or building block—of caveolae (from the Latin for "little caves"). Caveolae are flask-shaped invaginations on cell membranes. They were discovered in the 1950s, but it wasn't until the 1990s that researchers zeroed in on their role in cell signaling and signal transduction. At the time of these discoveries, Galbiati was a postdoc in the Albert Einstein College of Medicine lab of Michael Lisanti, who is at the forefront of caveolin research and one of the country's most frequently cited biologists.

When Galbiati came to Pitt in 2001, he began researching the role caveolin-1 played in cellular senescence, a naturally occurring state in which cells can no longer reproduce or divide. If enough of an organ's cells become senescent, the organ gradually loses function. Premature senescence, a kind of early aging of the cell, can be induced through oxidative stress, an insult brought on by exposure to free radicals, such as those found in ionizing radiation and other environmental agents. Galbiati's research showed that the presence of caveolin increased senescence during oxidative stress. So he decided to look at the role of caveolin in a classic oxidative-stress environment—cigarette smoking and COPD.

Along with Shapiro and other Pitt researchers, Galbiati found that gene-altered mice that produced no caveolin had less severe emphysema when exposed to cigarette smoke than mice with normal caveolin levels. The group found that caveolin in the mouse's lung cells activated the p53 pathway, an important series of cellular interactions that lead to cellular senescence. Caveolin-1 binds a p53 inhibitor, "hiding" it in the caveolae. Without the inhibitor to brake its development, the p53 pathway cascaded through the cell, leading to senescence and later on, to emphysema.

So, lower caveolin-1 levels, and thereby premature senescence, and you lower the rate of emphysema—simple, right? Not quite. Senescence, it turns out, isn't all bad. It slows down certain types of cancers. (Mutations in the caveolin-1 gene have been linked to breast cancer.) So by taking caveolin-1 out of the lung, you could limit emphysema but encourage lung cancer. Researchers need to ensure that any caveolin-related therapy for COPD does more good than harm, Galbiati says.

Galbiati's investigations into the link between COPD, oxidative stress, and senescence could provide a new way to understand the disease, says Shapiro, who has been on the front lines of COPD research for several years:

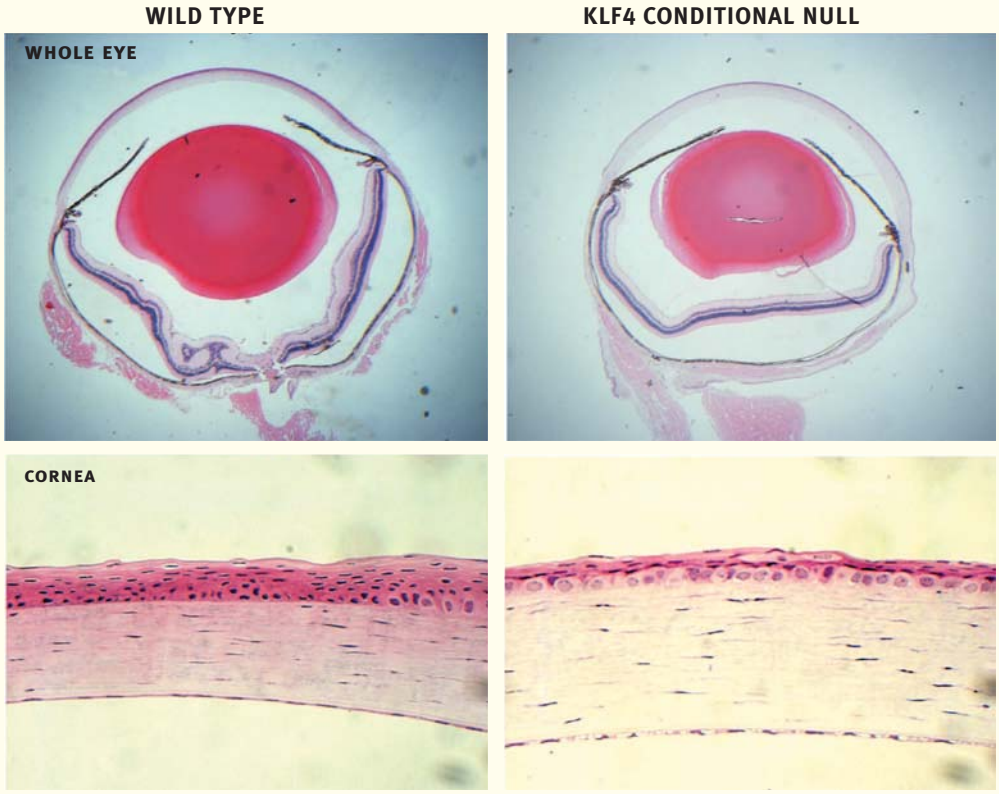
"He's really teased into some of the cellular mechanisms and signal transduction pathways" that initiate emphysema during smoking. "People are just starting to think about these things, so he's ahead of the game." ■

IF YOU CAN READ THIS,

THANK YOUR TRANSCRIPTION FACTORS

A NEW APPROACH TO WARDING OFF DRY EYE

BY ELAINE VITONE



COURTESY S. SWAMYNATHAN

Transcription factor Klf4 plays a key role in eye development and maintenance. Here, an animal study compares a normal eye (top left) and normal cornea (bottom left) with those of a mouse that lacks Klf4 (right column).

Every time you rub your eyes, a few cells in your cornea die. Without all the protective layers and health-promoting moistening mechanisms in your peepers, you'd be in the dark. But until recently, nothing was known about how these layers of protection form and stay healthy.

During his postdoc fellowship at the National Eye Institute, PhD Shivalingappa Swamynathan became interested in studying the role of gene regulation in eye development and maintenance.

"My colleagues found that transcription factors Klf4 and Klf5 were present in the cornea in high amounts," says the assistant professor of ophthalmology, "and yet nobody knew what they were doing." Two years ago, Swamynathan established the Laboratory of Ocular Surface Development and Gene Expression at the University of Pittsburgh to discover their role in the ocular surface.

In many organs throughout the body, Klf4 helps maintain a barrier to mitigate injury, it also keeps bacteria out and life-sustaining water and nutrients in. When you breed mice without Klf4, they die within hours—all the moisture in their bodies evaporates through the skin. This poses a problem if you want to study Klf4's role in the cornea, which doesn't fully form in mice until they're 6 to 8 weeks old.

In 2006, Swamynathan used bacterial CRE recombinase—a method of targeting a specific sequence of DNA and splicing it—to create a new strain of mouse that lacked Klf4 only in the lens, cornea, and conjunctiva portions of the eyes. In the case of the conjunctiva—a clear membrane over the white of the eye—the mice failed to form goblet cells—the cells that produce mucus, which protects and moisturizes the eye.

This finding could one day mean good news for patients with dry eye, a condition that affects as much as 45 percent of the population older than 65. Women are two to three times more likely than men to get it, and hormone-replacement therapy can make it worse. The irritation of dry eye is more than a nuisance—in time, it undermines the health of the cornea, which is vital to our vision. As the body fights to heal itself, the cornea can cloud with immune cells and scars. Eventually, dry eye can even lead to blindness.

A small number of dry-eye patients suffer from the condition out of a lack of goblet cells. And for many others, regardless of the underlying cause, if the condition continues for too long, it can *cause* the loss of goblet cells, fueling a vicious cycle.

Swamynathan used microarray analysis to identify more than 1,000 genes that Klf4 influences. He found that, of each of the five layers of the cornea, all are affected by these genes—from the outermost corneal protective barriers to the innermost corneal endothelium.

And that's just Klf4. Still to come are his Klf5 studies; he's breeding a line of mice for that now.

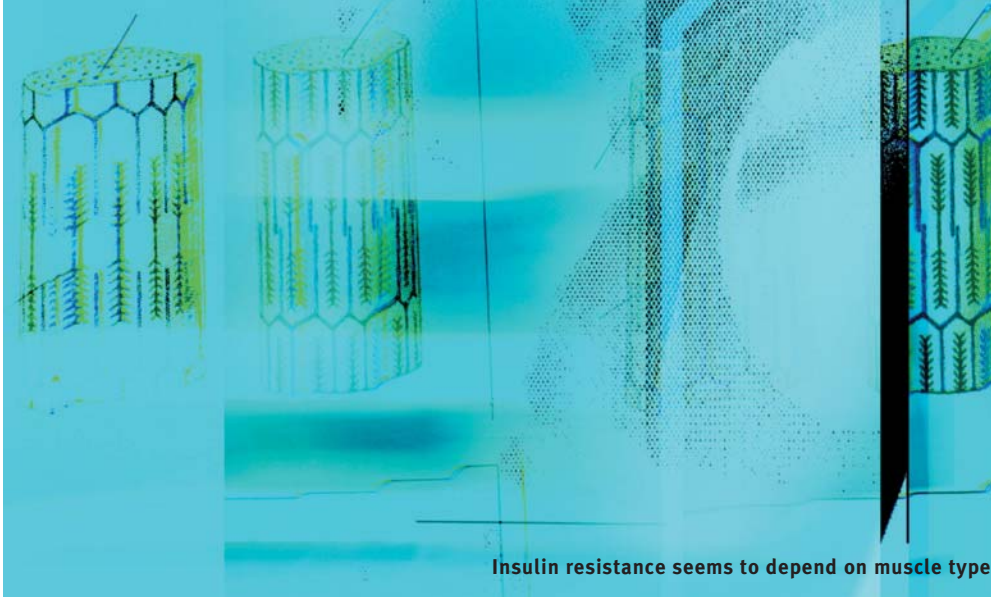
Klf4 and Klf5 are structurally similar and bind to the same sequence of DNA; however, their functions are very different. Klf4 is a suppressor of cell division and Klf5 an activator. Swamynathan looks forward to seeing how they complement one another and what happens when one is absent, or even both are absent.

"We have really a treasure trove of genes to study," he says, a glimmer of kid-in-the-candy-store in his voice.

"I will be characterizing these genes for the rest of my life." ■

GOODPASTER ON DIGESTIVE DOMINOES

BY SARA GOUDARZI



GETTY IMAGES

Insulin resistance seems to depend on muscle type

DIABETES: WHAT'S MUSCLE GOT TO DO WITH IT?

How well our skeletal muscles do their job seems to be a key factor in the development of type 2 diabetes. The specifics, however, are unclear.

Bret Goodpaster, a PhD associate professor of medicine at the University of Pittsburgh, thinks that insulin resistance depends on muscle type and its ability to accumulate potentially harmful lipids that affect sugar absorption.

We rarely think about how our bodies extract energy from food. After a meal, carbohydrates are absorbed into the bloodstream. The rest is pretty much a digestive domino effect: The pancreas secretes insulin, which attaches to cell receptors and activates other receptors to allow sugar absorption. The absorbed glucose is either oxidized or stored for later use.

At least, that's how it's supposed to work.

For about 23 million people in this country who suffer from diabetes, there's a glitch in the process. The pancreas of those with type 1 diabetes can't produce insulin. For people with type 2 diabetes—that's about 90 percent of all diagnosed diabetes cases—the pancreas secretes insulin, but it's either not enough or their bodies' cells don't respond to the hormone.

"It's not a case of insulin not being present, it's just not able to do what it needs to do to stimulate that glucose metabolism," says Goodpaster. Exactly why some people have this inability to respond to insulin has been a mystery to the scientific community, and one that Goodpaster hopes to solve.

A lifelong cyclist, Goodpaster has always been interested in exercise and human performance. He became more serious about the field when his father, at the age of 39, had quintuple coronary bypass surgery. Goodpaster was in high school at the time.

"I made the study of biology, health, disease, and exercise my passion and career," says Goodpaster.

Goodpaster has a master's degree in exercise physiology from Ohio's Kent State University and a PhD in human physiology from Ball State University, in Muncie, Ind. In addition to focusing on type 2 diabetes, he studies age-related loss of functional capacity and mobility.

Goodpaster takes advantage of novel methods, such as the acquisition of muscle and fat tissue from biopsies. By examining proteins and genes in skeletal muscle samples from human subjects, Goodpaster and his colleagues can translate findings back and forth from humans to animals and cell systems and models.

"We can literally look inside the muscle cells and see what might be some of the underlying mechanisms for this insulin resistance," he explains. "We have found that muscle cells accumulate a variety of lipids, some of which appear to be used as fuel for the muscle, whereas others appear to have a negative impact on the way the muscle effectively uses glucose."

He has recently begun to elucidate how diet and exercise seem to work at the muscle level in improving insulin resistance for type 2 diabetes.

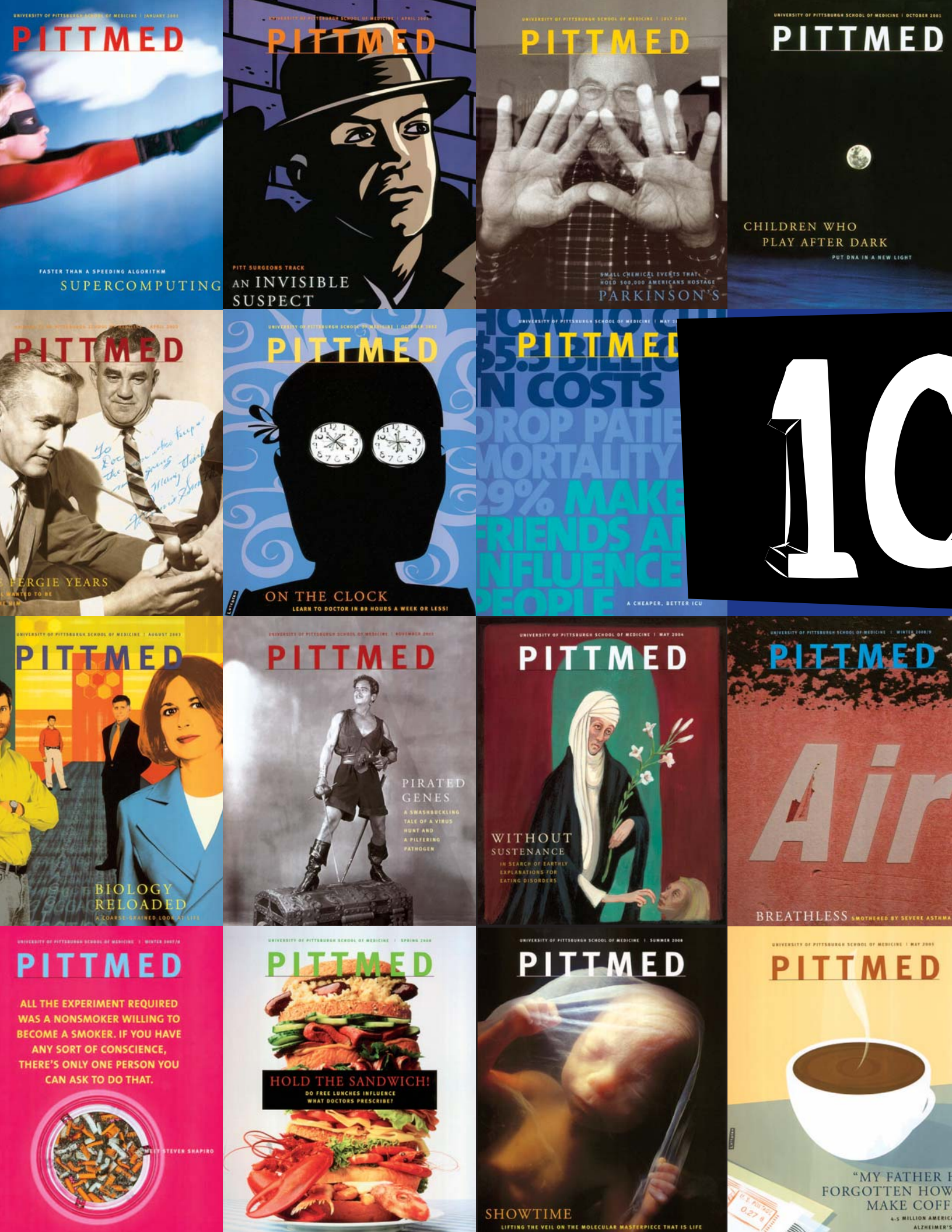
"[We] look at accumulation of lipids in muscle to see how this might be related to this fatty acid metabolism, mitochondria function, and then, in turn, how all this potentially plays a role in the development of type 2 diabetes," he says.

Earlier this year, Goodpaster and his team convincingly showed that when older adults lose weight by dieting alone, they also lose significant amounts of muscle mass—which could affect their mobility and independence. But when they combine calorie restriction with exercise, they can nearly completely prevent that loss of muscle associated with dieting.

His group is also one of the few in the world to use positron emission tomography to look at insulin resistance in glucose metabolism of skeletal muscles. In his study, volunteers are infused with a radioactive tracer that emits positrons when glucose is metabolized; that way, researchers can pinpoint locations in the body where it's metabolizing. Physicians typically use this technology in cancer patients to determine whether a tumor is active based on how much glucose it's breaking down.

"We're essentially doing the same thing, except in fairly healthy people, looking at glucose metabolism in muscle response to insulin to see if we can get more mechanistic information about their insulin resistance," Goodpaster says.

This mechanistic information, Goodpaster hopes, will help the digestive dominoes fall into place for the 8 percent of the population suffering from type 2 diabetes. ■


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LIFTING THE VEIL ON THE MOLECULAR MASTERPIECE THAT IS LIFE
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"MY FATHER
FORGOTTEN HOW
MAKE COFF

A DECADE OF PITT MED

BY MAGAZINE STAFF AND CONTRIBUTORS

For Ten

For 10 years now, we've followed around doctors walking dark city streets to care for the homeless, bioengineers convinced they can find a way to help veterans regrow limbs, students who'd happily travel several thousand miles to help children orphaned by AIDS. Our days are spent witnessing generosity and genius and mourning and triumph and humility and astonishing aplomb.

As vocations in which practitioners grapple with issues of humanity and mortality as part of a daily routine, or at least as a daily backdrop, medicine and biomedical science are awfully good realms for story fodder. Remember high school English, when Mrs. Finkelbottom taught you about the great themes of literature? You know—Man v. Man, Man v. Nature ... Well, we decided to see how some of the more compelling stories we've told have evolved and how they might fit into such a roster. With apologies to Homer and Hemingway (and with a decidedly medical twist), here goes. Ten years, 10 enduring themes of literature. Thank you for the chance to revisit these characters—and for a fascinating decade.

—Erica Lloyd, Editor in Chief

HEADLINE TYPOGRAPHY | MICHAEL LOTENERO

TO SEE PREVIOUS ISSUES, GO TO OUR ARCHIVES AT **http://pittmed.health.pitt.edu**

Man V. Man

When we met with Paula Monaghan-Nichols for this magazine's very first cover story, she was trying to avoid being bitten by a monster of her own creation ("Killer Mice," October 1999). The uncooperative, genetically engineered baby mouse was the runt of the litter, a mutant with a gene called *tailless* knocked out. Imagine a baby rodent Hannibal Lecter, though not so clever. Her mouse had learning deficits, was fearless, and was, most notably, extremely aggressive. By the time it reached sexual maturity, if left alone with its brethren, it would have fought them to the death and won.

It was natural to wonder, what might such a nasty creature tell us about ourselves?

The mouse and others of its kind are giving us clues as to how we're wired. In the past decade, Monaghan-Nichols, an associate professor of neurobiology at the University of Pittsburgh, has discovered that *tailless* is involved in the production of stem cells. So knocking the gene out of all the brain cells seriously tampered with its developmental pathways. The gene is important to restoring cells in the brain and could hold clues for how certain regions might rebuild from degenerative conditions.



In 1999 we asked, what might a psychopathic mouse tell us about how we're wired?

Monaghan-Nichols later decided to delete *tailless* more selectively. She targeted the cerebral cortex and ended up with much friendlier mutants—not a mean mouse among them. Still, like the knockout mice she bred 10 years ago, these critters aren't at all anxious or fearful.

She was surprised to find that although the mice have much smaller hippocampal formations, that hasn't seemed to have affected their ability to figure out maze puzzles. The hippocampal structure has long been associated with learning and memory. "The hippocampus looks so different from normal, but the animals perform extremely well," she says.

Other knockout animal models, including smaller critters like zebra fish, fruit flies, and the nematode *Caenorhabditis elegans,* are being used throughout the school in powerful ways. *C. elegans*, for example, has helped Gary Silverman, professor of pediatrics and chief of the Division of Neonatology and Developmental Biology, in his studies of a serpin gene, which is protective in epithelial cells in the intestines and lung. We first wrote about his work and worms in November 2004 ("At the Boundaries of Hope"). Now Silverman's microscopic serpin knockout worm is a "workhorse" for drug discovery, as he puts it.

Just a few years ago, researchers were thrilled at the prospect of using live cells in robotic drug discovery systems to look for promising therapeutic compounds. Silverman and his colleagues have refined techniques for using live animals, namely his favorite nematode, to search for an antidote for necrotizing enterocolitis, a condition in which the intestinal wall dies in newborns. "We have a tool that will permit us to identify a drug for a disease that has no known treatment," he says.

"This is an animal that has a full neurologic system," adds Silverman; so his team will know right away whether a compound is toxic. And they can put 50 animals in a microtiter well at once. "That's like screening 50 patients!

"We think this [serpin] pathway is well conserved in worms and extends all the way up to humans," he says.

Likewise, Monaghan-Nichols' *tailless* models continue to intrigue her: "There's no doubt to me that there is a primordial [*tailless*] gene that performed a primordial function and that our proteins have somehow evolved from that." Her knockout mice may even one day give us insight about man's inhumanity to man, or at least how anatomical and other deficits can influence behavior. If she deletes *tailless* from certain regions outside the cortex, she has reason to believe that "maybe the aggression will come back." She hopes so, anyway. —*EL*

the Individual in Nature

"We started out being virus hunters," Yuan Chang told *Pitt Med* in 2003, when asked what had attracted her and her husband, Patrick Moore, to the School of Medicine ("Pirated Genes," November 2003). They wanted to continue the quest, she said, and Pitt offered a chance. "We may not find anything," she warned then, but that disclaimer proved unnecessary. In 2008, they used molecular techniques to show that a virus was behind a rare cancer called Merkel cell carcinoma. This came 15 years after they had discovered the Kaposi's sarcoma herpes virus.

Moore is a professor with appointments in microbiology and molecular genetics in the School of Medicine, as well as in infectious diseases and microbiology in the Graduate School of Public Health. Chang is a professor of pathology.

We photographed the pair lording over a treasure chest and gazing off into the distance. Like all explorers worth their salt, they appear ready to sail into the unknown. Theirs is a classic story of delving into the natural world and returning with treasure.

But the pursuit of these viruses that have forever been part of nature took place not in the field but in a sophisticated molecular biology laboratory using cancerous tissue samples. The use of the built environment to explore the natural history of viruses has expanded greatly at Pitt in recent years.

Pitt's Center for Vaccine Research was launched in 2006 (see our "New Math" story from that November), and it has brought a whole new area of expertise to the University. Its centerpiece is the federally funded Regional Biocontainment Laboratory, which takes up an entire floor of the University's Biomedical Science Tower 3. The lab is rated Biosafety Level III, meaning Pitt researchers can study highly infectious agents such as tuberculosis, dengue fever, influenza, and HIV. Before the lab was built, approximately a half-dozen investigators at Pitt worked in these areas. When the center is fully staffed this fall, there will be 18.

Most notable among the scientists who joined the effort at Pitt is Donald Burke, director of the center, associate vice chancellor for global health, and dean of Pitt's Graduate School of Public Health. Burke is an expert on infectious diseases and biodefense who previously was in charge of military infectious disease research at Walter Reed Army Institute of Research. From early in his career, he has seen the value of computer models used in fields as disparate as economics and engineering, and he has championed and advanced their application to understanding the spread and control of infectious diseases. Pitt investigators like Burke and Bruce Y. Lee (an MD/MBA assistant professor of medicine, epidemiology, and biomedical informatics) have created computer models to help inform policy makers on public health issues. One model contains data points to represent each person in the United States, complete with demographic data. Scientists can enter data related to outbreaks such as the current H1N1 influenza and see the scenarios that could result from such interventions as mass vaccination or limited vaccination.

Thus, questions that would otherwise require a massive natural experiment on a long timeline are quickly explored in the artificial world of the model. —*Chuck Staresinic*



Patrick Moore and Yuan Chang continue to come back with the loot. (Here, they are shown in 2003.)

the Individual in Nature

We used to think of cancer as a foreign invader, a regimented type that overtook one organ after another in an orderly sequence. The thinking was: Find the tumor and cut it out, along with as much surrounding tissue as you can. And if the cancer came back? Well, you just didn't do it right, Doc. Through the first half of the 20th century, cancer literature often read more like radical-surgery how-to manuals than reports on scientific investigation.

Today, we know that cancer is not a foreign intruder, but a disease that lives throughout the body as a whole, traveling the bloodstream and planting new growths wherever it happens upon the right circumstances. We understand that we can't fight it without applying a nuanced understanding of our own biology and the nature of the disease (see "Bad Company," Fall 2008).

In our July 2002 issue, *Pitt Med* interviewed the front man of the very first clinical trials for cancer that, in 1967, finally laid to rest the radical-surgery paradigm ("Bernard Fisher in Conversation"). Fisher's studies set the precedent for the University of Pittsburgh Cancer Institute's (UPCI) growing clinical trial program—now more than 200 active trials strong—and, arguably, the very notion that the science of cancer treatment should be based in (go figure) *science*.



Fisher (MD '43) went on to lead studies of the breast-cancer drug tamoxifen, the first biologically based treatment for cancer, which is still widely used today. In 1998, tamoxifen was found not only to stave off breast-cancer recurrence, but also prevent it from forming in the first place.

Last winter, as part of the centennial commemoration of the American Association for Cancer Research, the editors of *Cancer Research* invited Fisher to write an article detailing the evolution of cancer surgery, and his role in it, for the December issue of the journal.

In February, Pitt honored Fisher when Nancy Davidson, UPCI's new director, gave a presentation as part of Fisher's namesake lecture series. University officials presented him with an honorary degree and played a video tribute to him and his legacy. The event also marked the 90th birthday of this influential scientist, who took on the doubly taxing role of translational researcher before it had much meaning—or much clout.

"The surgeons would say, 'Oh yeah, Bernie Fisher—that rat doctor,'" Fisher recalled with a laugh in the tribute video. "The basic scientists said, 'Oh yeah, Bernie Fisher—the surgeon.' I had a disconnect of who I was and what I was. And that's survived pretty well over the years."

—Elaine Vitone

SINGLE CANCER CELL SEEKS MULTIPLE PARTNERS. AMBITIOUS, HYPERACTIVE, UNSTABLE MUTANT WITH NOMADIC TENDENCIES. REPLY AT YOUR OWN RISK GOOD AT FITTING IN (FOR A WHILE). INTERESTED IN HAVING LOTS OF OFFSPRING.

Taking on cancer today is less about radical surgery and more about understanding the disease's very nature, thanks to early visionaries like Bernard Fisher (shown above).

the Individual v. Himself

In literature, the tragic hero's downfall is his failure to recognize his own fatal flaw. Throughout the history of psychiatry and neurobiology, too, we've struggled to glimpse at frailties within the living brain—to peer inside and understand what brings about some of the most profoundly heartbreaking disorders. Imaging technologies are revolutionizing our understanding of the brain, still many psychiatric conditions, including psychotic disorders and neurodegenerative diseases, remain difficult to reckon with—patient exams and intake interviews being the only diagnostic tools available in the clinic. But emerging research may soon help bring these blind spots to light, both figuratively and literally.

A team at Pittsburgh Institute for Neurodegenerative Diseases (PIND) is working to better understand and treat Parkinson's and other neurodegenerative diseases. Assistant professor of neurology Sarah Berman develops new techniques for studying the critical processes of mitochondria, which have defects in the dopamine cells of Parkinson's patients. And an animal study of a gene therapy for Parkinson's is under way, led by J. Timothy Greenamyre, professor of neurology, chief of the Division of Movement Disorders, and director of PIND, and Edward Burton, assistant professor of neurology and of microbiology and molecular genetics.

Basic science studies and autopsies are bringing schizophrenia's disease process into focus, says David Lewis, professor of psychiatry and neuroscience and director of Pitt's Translational Neuroscience Program and Conte Center for the Neuroscience of Mental Disorders.

Schizophrenia is best known for its characteristic hallucinations and delusions, but an even more devastating side of the disorder is cognitive impairment. Psychosis comes and goes, but cognitive impairment is constant, progressive. It's the best predictor of how functional these patients will be. In "A Chance for Normalcy?" (May 2006), Lewis told us his team had discovered that GABA neurons—neurons that regulate working memory—function improperly in people with schizophrenia.

Last year Lewis completed a proof-of-concept trial for a compound that boosts the signal of these neurons—potentially the first drug to treat schizophrenia's cognitive symptoms. Officials at the National Institute of Mental Health were so encouraged by the biological rationale for this approach they began a multicenter clinical trial before Lewis' study was complete. NIMH trial results are expected to be released in late fall.

Alzheimer's is another disease that has long eluded researchers, its telltale amyloid plaque deposits until recently only visible in the brain through autopsy. In May 2005, when *Pitt Med* did a roundup of science's understanding of Alzheimer's and



In May 2005, writer Cindy Gill shared a story full of love and heartbreak about her Alzheimer's-stricken father, who had forgotten how to make coffee.

Parkinson's ("Stolen Lives"), one of the most promising breakthroughs was a dye that makes amyloid plaque visible in the PET scans of living subjects. The dye had been developed the previous year by Pitt researchers Bill Klunk (professor of psychiatry, codirector of Pitt's Alzheimer Disease Research Center, and director of the Laboratory of Molecular Neuropharmacology at Western Psychiatric Institute and Clinic) and Chet Mathis (director of the UPMC PET Center and professor and vice chair for research in Pitt's Department of Radiology). Dubbed Pittsburgh Compound B (PiB), the dye has been instrumental in thousands of Alzheimer's studies around the world. Surprisingly, these studies have shown that not everyone who has significant amounts of amyloid plaque has Alzheimer's. What other mechanisms are involved? Klunk hopes to find out. His team follows patients with a rare, genetic form of Alzheimer's. Scans from these patients' presymptomatic years will offer a rare glimpse at the disease pathology before amyloid plaque starts to form—and eventually, Klunk hopes, a target for therapy.

Yet PiB has a half-life of only 20 minutes. In the fall, GE Healthcare will begin phase III clinical trials for a more stable version that can be used in the clinic.

"In my future view," Klunk says, "I see people getting their colonoscopy at 50 and their amyloid scan at maybe 65. And if you have amyloid plaques, we hope to have a drug to get rid of it. It's not enough until we get that second part." —*EV*

the Individual v. Himself

"Did I kill the old hag? No, not the old hag—I killed myself!"
—Raskolnikov in Dostoyevsky's *Crime and Punishment*

Hamlet, *Strange Case of Dr. Jekyll and Mr. Hyde*, *Heart of Darkness*—the classics abound with tales of the individual battling against himself, suffering the grim consequences of his actions. It's a recurring theme in medicine, too. In fact, the prevalence of autoimmune diseases like diabetes—illnesses in which the immune system attacks the body's own tissue—appears to be increasing worldwide. But Pitt scientists are devising creative solutions that could help reverse this trend.

Few diseases are as complex as type 1 diabetes, in which the body mercilessly attacks the pancreatic beta cells responsible for producing insulin. But Massimo Trucco, Hillman Professor of Pediatric Immunology and an MD professor of pediatrics, pathology, human genetics, and epidemiology, and Nick Giannoukakis, an associate professor of pathology and immunology, are duping the very immune cells that sicken patients. *Pitt Med* first started tracking this work in our January 2000 issue, and in the summer of 2008 we wrote about an upcoming safety trial involving engineered immune cells.



ousin of jellyfish could d clues for suppressing the mune response.

The scientists have completed treatment and a yearlong follow-up of seven of 14 adults with diabetes for this trial. They remove dendritic cells from the patients' blood and prime them with molecules that render them incapable of initiating an autoimmune attack. Then they infuse the modified cells back into the body. "The good news is that we see absolutely no side effects," Giannoukakis says of the trial so far. Now the two are gearing up to test a more streamlined form of their therapy—one that relies on injections of tiny primed beads, eliminating the need for tedious dendritic cell removal—in safety trials next year. "I think we're going to have some exciting data coming out in the next three to four years," Giannoukakis says.

Halting the immune attack may not suffice, though—especially if the disease has already killed many beta cells. Some patients will also require pancreatic islet transplantations, but they aren't easy to achieve: One transplant can require tissue from up to six different pancreases, and sometimes repeat surgeries are necessary. To address this problem, Andrew Stewart, chief of Pitt's Division of Endocrinology and Metabolism, is developing beta cells that can regenerate themselves over and over again—which these cells wouldn't normally do. Working with him from his division are Adolfo Garcia-Ocana, a PhD associate professor; Rupangi Vasavada, a PhD assistant professor; Nathalie Fiaschi-Taesch, a PhD assistant professor; and Karen Takane, a PhD research associate.

Oddly, Stewart stumbled upon the idea while researching a calcium-regulating protein implicated in osteoporosis. The pancreas made this protein, too; when it made too much, there were "way too many beta cells," he noticed. Stewart is studying 30 known growth-regulating proteins to see whether tweaking them could boost beta cell replication. So far, he's identified a few. His team "doesn't make beta cells," he explains. "We make them better."

It would be ideal, of course, to prevent such diseases from developing at all—but first scientists must understand the biological pathways involved. This is the purview of Richard Duerr, associate professor of medicine and human genetics, whom we first wrote about in our July 2001 issue. Duerr and his colleagues, as part of an international consortium, are identifying genes involved in inflammatory bowel disease (IBD)—a condition that includes Crohn's disease and ulcerative colitis. (Duerr notes that IBD isn't an autoimmune disease, because the immune system isn't fighting its own cells. Instead, it mounts an overaggressive response to GI bacteria. Yet, the concept is similar.) Since 2001, Duerr and colleagues have found more than 30 gene variants associated with risk for the development of Crohn's. These discoveries have implicated biological processes previously not known to be involved in Crohn's, such as autophagy, the process by which cells recycle their old and damaged bits and break down intracellular bacteria. Autophagy may go awry in IBD and "lead to chronic tissue damage in the GI tract," Duerr explains.

Our greatest foes might well be within us, as Spanish novelist Miguel de Cervantes Saavedra once noted. But that doesn't mean we can't win. —*Melinda Wenner*

When Josh Maloney connected the blasting cap to the quarter-stick of dynamite in his hand, the circuit was supposed to be broken. This one was faulty and closed from the get-go. Two tours of duty in Iraq without so much as a cold, and he blows his hand off during a training exercise in Quantico, Va.

Days later, when he finally regained his wits at Walter Reed Army Medical Center in Washington, D.C., Maloney knew that he wanted to be in Pittsburgh. It wasn't just home. Pittsburgh represented the medical expertise he wanted.

Maloney, a Marine corporal at the time, had no idea just how appropriate his hometown was. Two years earlier, *Pitt Med* had written about W.P. Andrew Lee ("When Being First Isn't Enough," November 2005), Pitt professor and chief of plastic and reconstructive surgery. We described Lee's interest in hand transplantation—a feat he had not yet attempted, though a few dozen transplants had been tried around the world. Lee felt that scientists did not yet know enough about achieving tolerance—convincing the immune system to accept new biological material as self—to attempt hand transplantation.

"I will be disappointed if we don't make meaningful progress on tolerance induction in five years," he said then. In April 2009, Lee led a team that gave Maloney a new hand. They followed that up several weeks later with the first double hand transplant in the United States, this one for a Georgia man who lost his hands to a sepsis infection a decade earlier.



Early in his career, transplant great Thomas E. Starzl seemed to be his own worst enemy.

The hand transplants involved a novel approach to suppressing the immune system that was developed here. Dubbed the Pittsburgh protocol, it involves an infusion of antibodies on the day of the transplant and, 15 days later, another of bone marrow from the deceased donor. The patient then takes a low daily dose of one antirejection drug instead of the more typical three-drug cocktail that carries a higher risk of side effects like diabetes and infection.

"This is similar to what has been done here with patients who have had kidney transplants," says Fadi Lakkis, professor of surgery and immunology and scientific director of the Thomas E. Starzl Transplantation Institute. In the short term, it's clear that these patients do as well as patients on two or three drugs, and they have fewer side effects from their drugs, says Lakkis. What remains to be seen is what happens after three to five years. Will these patients be at higher risk of chronic rejection or delayed loss of the grafted organ?

For patients, transplantation is a long battle against the self—a high-stakes attempt to trick, cajole, distract, or beat down the immune system until it finally accepts new tissue as self. Surgeons have been known to battle the self, as well. Thomas E. Starzl, for one, once seemed to be his own worst enemy. Working since the 1960s to make liver transplantation a viable option for otherwise doomed patients, Starzl developed a monomaniacal drive. His health suffered. Some said he was crazy to try this thing that would never work. Colleagues learned to climb aboard or get out of the way.

As this magazine recounted one of Pittsburgh's epic and storied efforts ("Only Starzl Dared To," May 2006), the surgeon and Pitt Distinguished Service Professor of Surgery eventually succeeded in shepherding liver transplantation into the realm of the possible. When he finally stepped back, there was a thriving field of medicine where only a makeshift outpost had stood before.

His next goal: drug-free tolerance. How close are scientists to achieving that today?

"You are catching me at a pessimistic moment," says Lakkis, with a laugh, before explaining the successes and shortcomings in transplantation research.

He says "the field is not any closer [to drug-free tolerance] on a large scale" than when this magazine covered the topic in our Fall 2006 issue ("Break on Through"). "It is a little closer in terms of small scale. It remains an unpredictable process. You can achieve tolerance in a small number of patients, but we still don't know how you can identify that small group of patients ahead of time." That said, Lakkis rattles off the details of recent promising research endeavors at the Starzl Institute, including labs that modify dendritic cells and antibodies to turn down the immune system.

Lakkis has a more fundamental approach. He studies the primitive immune system of *Hydractinia*, a relative of jellyfish, which detects foreign tissue and attacks it. Despite 800 million years of evolution separating us, humans share some aspects of this innate immune system, which may act as a sort of alarm system to alert our more evolved adaptive immune system to foreigners. Lakkis, along with colleagues at Pitt and Yale University, has identified a *Hydractinia* gene involved and is now looking for human genes that are structurally similar. The scientists hope to define a new mechanism in our innate immune system for identifying foreign tissue. If they find one, it would help demonstrate why transplantation's battle against the self is so protracted—because living things have been protecting this sense of self for at least 800 million years, and probably much longer. —*CS*

The Individual in Society

"True strength lies in submission which permits one to dedicate his life, through devotion, to something beyond himself."
—Henry Miller, *The Time of the Assassins*

Brian Miller is a rare doctor who doesn't wait for patients to come to him; instead, he goes to them, seeking out people in need on the streets, in remote communities, and in their homes. Miller (MD '06), a resident in family medicine at Pitt whom we profiled in the February 2004 issue, says his medical philosophy was shaped by his experiences in the Geriatric Experiences for Medical Students (GEMS) program while a Pitt medical student.

"It made me realize that in the clinic, you really are only seeing a very small piece of what a patient's life is like," Miller says.

Through GEMS, Miller visited geriatric patients in their homes, and his experiences revealed that patients sometimes mask their problems in public. "A lot of my patients get dressed up, groomed up, to come to the clinic, looking their best as they walk through the door," he explains. "Things are often quite different at home." For example, he recently paid a visit to a stroke patient who was not recovering well. "I got to see a little bit about who he was—the golf clubs he had used every day that he's no longer using," Miller says. The contrast between his once happy-go-lucky life and his current plight suggested to Miller that the patient was probably depressed. Now, with proper treatment, the patient "has gotten some of his pep back," he says. Ultimately, Miller explains, when doctors see patients at home—something he plans to do throughout his career—they catch unique glimpses of their lives that provide insights into how best to treat them and prevent future health problems.

Miller also reaches out to other communities. This spring, he spent a month in Arizona working at a hospital affiliated with an Apache reservation. And he's a part of Operation Safety Net, a group of physicians and students with a mobile clinic that travels around Pittsburgh treating homeless patients.

A Pitt experience also helped Brad Dicianno make his unique mark as a physician. Dicianno (MD '01), who participated in Pitt's Area of Concentration (AOC) program in disabilities medicine, is now an assistant professor in the Department of Physical Medicine and Rehabilitation, director of the department's Spina Bifida Outpatient Clinic, and the medical director of the Center for Assistive Technology. He builds control interfaces like joysticks to help people with disabilities—especially those with debilitating complications, such as tremors—more easily operate computers and power wheelchairs. In addition, he is building a "virtual environment" that will assess patients' motor abilities so that he can design custom interfaces suited to their strengths. Ultimately, says Dicianno, who was profiled in our April 2001 issue, "the AOC really did make a difference in exposing me to the needs people have that can be met by technology." *—MW*



J. Nadine Gracia in 2000.

In her medical school interview, J. Nadine Gracia said that she wanted to eventually play a role in forming health policy, recalls Paula Davis, Pitt's assistant vice chancellor for health sciences diversity. It would be difficult to find anyone who followed through on a statement more thoroughly or more successfully in just a decade.

Gracia (MD '02, Res '05) was president of the Student National Medical Association during med school (we first wrote about her in January 2000, "President in Training"), and she is currently a White House Fellow, a program that includes Colin Powell and Wesley Clark as alumni. Gracia works on projects addressing women and girls' health in the outer Pacific Islands. As an assistant to the counselors to the U.S. Secretary of Health and Human Services, she prepares briefs and informational memos to guide policy decisions and leads a departmental work group on the insular areas.

Mentors at Pitt made it possible for her "to be a national leader and a medical student at the same time," Gracia says.

"I received the same level of support at Children's Hospital," she says of her residency experience. "They knew I cared about leadership roles and advocacy." *—CS*



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nonoxide and nitrite are
evealing their good sides.

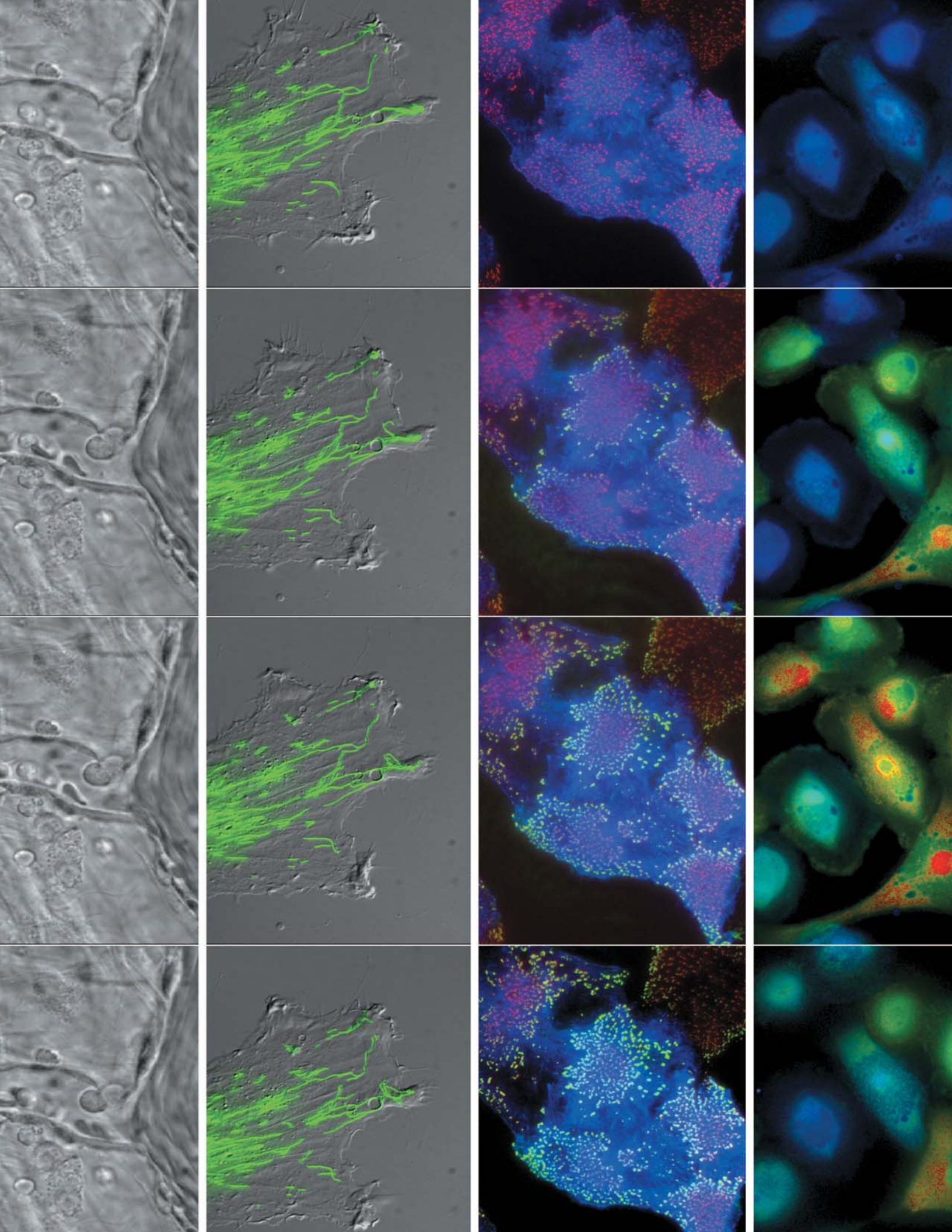
It's shocking to see the younger generation swoon over characters that their elders once wanted locked up. But in the unpredictable world of biomedical research, that is the case with toxic molecules like carbon monoxide (CO) and nitric oxide (NO). They are free radicals—the same ones found in cigarette smoke and automobile exhaust. We've been warned about them, but in the past 10 years, *Pitt Med* has devoted a lot of ink to describing how once-maligned molecules are now studied for their beneficial effects.

A presentation at Science 2008—Pitt's annual science celebration and biomedical mixer—was titled "NO, NO, a Thousand Times NO!" Moderating the program was Bruce Freeman, PhD professor and chair of pharmacology and chemical biology at Pitt, who has spent a few decades at the leading edge of free radical biochemistry. On the docket were four experts in cellular signaling, all Pitt clinicians. One surgeon described how NO was administered to protect his patients' new livers from damage during and after transplantation. And Mark Gladwin, professor of medicine, claimed that our blood cells derive cardioprotective NO from nitrate and nitrite—maligned molecules culled from our drinking water and present in that most evil of foodstuffs, the hotdog. You might recall Gladwin and Freeman's heretical hypothesis from our previous issue ("Welcome to the Dark Side," Summer 2009).

Pitt professor and Department of Surgery chair Timothy Billiar runs a lab that has made real progress on the NO puzzle ("An Invisible Suspect," April 2001). In the late 1980s, his lab showed that an enzyme that catalyzes the formation of NO from oxygen and arginine was expressed in liver cells. He and his colleagues in surgery have since explored the complex regulation and function of this enzyme—called iNOS, for induced nitric oxide synthase—in the liver. In some settings, iNOS contributes to liver damage; in other settings, it protects liver cells from death. The Billiar lab also actively explores the action of NO and iNOS in hemorrhagic shock, sepsis, cell signaling, and programmed cell death.

Elsewhere in surgery, associate professor Noriko Murase is using CO to protect kidneys during experimental models of kidney transplantation and is set to begin a clinical trial in patients this year.

What was once a rogue's gallery of toxic molecules is becoming a physiological hall of fame. Pitt scientists are overseeing big parts of the changeover. —*CS*



the Individual and Technology

"It's almost intelligent, almost sentient," Simon Watkins says with amazement, even though he's watching something he sees every day.

Watkins—PhD professor and vice chair of Pitt's Department of Cell Biology and Physiology, as well as director of the University's Center for Biologic Imaging (CBI)—talks as he runs one of hundreds of cell-in-action videos on his computer. The video is captured from a confocal microscope and a camera recording 150 frames per second. On the screen is a dendritic cell in action. It spreads out in three dimensions, forming what appear to be feet. The feet stretch out and engulf a bacterium, and the dendritic cell internalizes it.

Watkins, Pitt's guru of scientific imaging, arrived here in 1991 and, since then, he says, "The whole field and my existence have changed completely. We can now image so much faster, deeper, and with more colors simultaneously." *Pitt Med* assembled a photo essay featuring the CBI in 2000. It was amazing stuff at the time, says Watkins, but "it was all dead material and all in two dimensions." Today's high-speed, three-dimensional images, he says, represent a sea change. And seeing things happen live and in real time—from a single molecule to a whole cell—provides something invaluable to Watkins: context.

On his rounds of various conferences, Watkins often brings with him a recording of a Steelers game. In the still shot he shows first, quarterback Kordell Stewart is under center at the goal line.

"We can hypothesize what's going to happen next, but we don't know," Watkins says. "You're just looking at a slice of time. A frozen section of time." When the film rolls, Stewart takes the snap from Dermontti Dawson and leaps into the end zone.

But without the context that time provides, you get hypotheses like this:

"A Russian guy comes up to me," recalls Watkins, "and I asked him, 'What do you think is happening?' There was silence. Then he said, 'What I saw was very large men wearing tight, yellow pants. I thought [Stewart] was actually milking [Dawson].'"

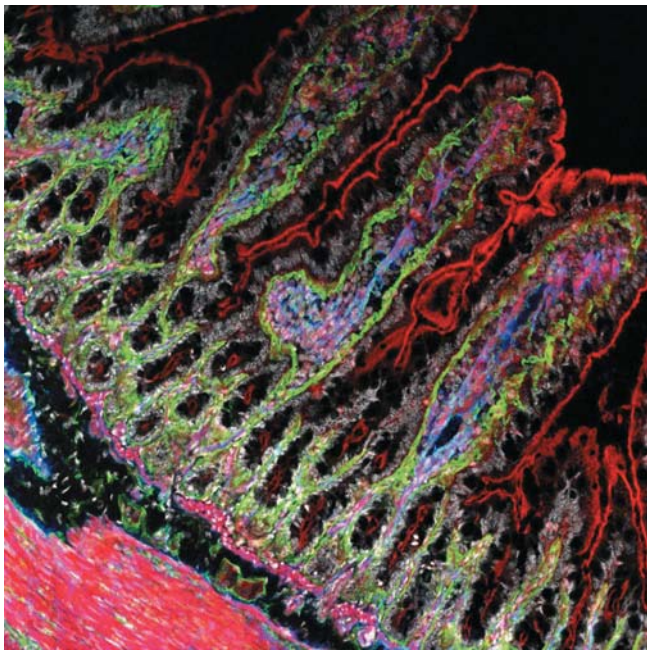
Watkins and the cadre of scientists served by the CBI are also using new technologies and techniques to image living animals. Beating fish hearts and the working pancreas of a rodent have been captured in three dimensions and in real time. Next up, Watkins says, is an entire, living animal.

Not far from Watkins' technological emporium in the Thomas E. Starzl Biomedical Science Tower, Angela Gronenborn does a different kind of imaging, a form of seeing beyond the realm of visible light ("Dark Arts," February 2006).

Gronenborn, a PhD and UPMC Rosalind Franklin Professor as well as inaugural chair of Pitt's Department of Structural Biology, is dedicated to solving the structures of proteins, molecules, and viruses. In 2007, Gronenborn was named head of a National Institutes of Health–funded, $16 million Center for HIV Protein Interactions, based at the University of Pittsburgh. Subsequent work related to that project, Gronenborn says, has resulted in nailing down the structure of the HIV capsid—its protein shell. Her lab also discovered and laid out the structure of a protein, cyanovirin-N, which boasts antiviral properties. These are steps, she says, toward finding vulnerabilities in HIV and possible tools to attack those weak spots.

"I really do believe that we will get the atomic structures of entire cells within the next 10 to 15 years," she says. "The technology is getting there. Also, the architecture and atomic detail of an entire virus—and they're smaller than entire cells—is in reach. People say I'm crazy, that it's science fiction, but I think it will happen." —*Joe Miksch*

LEFT: Simon Watkins has collaborated with Pitt colleagues to see (left to right columns) blood flowing in a live rat (Flordeliza Villanueva's lab), mitochondria in action (Luis Ortiz), a cell having a snack through endocytosis (Linton Traub), and calcium activity in a dendritic cell (Russ Salter).



A section of fixed, frozen mouse intestine imaged a decade ago. Watkins notes, "It is very pretty, but there is no movement, and it's only two dimensions."

Nothing like this had ever been done.

In November 2003, Pitt surgeons revealed to a stunned audience at a neurosurgery conference that they had performed more than 300 minimally invasive brain surgeries through the nose.

Carl Snyderman, professor of otolaryngology and of neurological surgery, and Amin Kassam, former chair of neurological surgery, coined the term "expanded endonasal approach" for the technique that allowed them to reach across the entire base of the skull. Pitt surgeons now routinely reach as far back as the top of the spine, out to the mandibular joint on either side, and forward to the brow.

The discipline, says Ricardo Carrau, professor of otolaryngology and of neurological surgery, "has become a subspecialty, and it's very competitive."

With industry partners, the surgeons have developed a prototype simulator that gives proprioceptive feedback: "When you bite into tissue with an instrument, you want to feel whether you are biting bone, or soft tissue, or tumor," Carrau says.

When we first reported on this technique (May 2005, "Twin Portals to the Brain"), a common postsurgical complication was leakage of cerebrospinal fluid through the opening breached in the base of the skull. Then surgeons reconstructed this barrier using fat or other soft tissue. They now apply a flap of tissue excised from the nasal septum. Because the tissue includes blood vessels, the graft takes to its new home much better than fatty tissue. Previously, says Carrau, "15 to 30 percent of patients needed a second surgery for repair of the leak. Nowadays, it's about 4 percent." —*CS*



Holy numbers, Batman! Using a supercomputing system called "Bigben," Pei Tang's (not shown) group processes data describin 160,000 atoms daily. When we wrote about her studies in 2001, data from 68,000 atoms took 10 days to process. All this crunchi is allowing Tang to reveal how anesthetics work.

the Individual and Technology

Pei Tang knows it takes more than one punch for anesthetic drugs to knock us unconscious. In 2001, we described how Tang, professor of anesthesiology, used the Pittsburgh Supercomputing Center to model the interactions between the anesthetic halothane and a simple ion channel. The number of atoms in her system, 38,724, was considered huge at the time. Now, Tang's group is using "Bigben," a supercomputing system she calls "revolutionary," to model more complex and realistic scenarios. Her postdocs and students feed data from more than 160,000 atoms into Bigben daily, using larger proteins and a wider variety of anesthetic drugs to visualize 20–30 nanoseconds of cell-membrane activity. Multiple models are giving them a clearer picture of what happens at the molecular level under anesthesia. Transmembranous neurotransmitter receptors are like doors to our brain cells. When an anesthetic latches onto a neurotransmitter receptor, the door becomes warped, and neurotransmitters can't function properly. Tang hopes to soon combine her computational and experimental studies to develop safer and longer-lasting anesthetic drugs. *—Brandon Ellis*

With childlike glee, Marco Zenati moves a Microsoft videogame joystick and points to a computer-generated image of a beating pig's heart. "See the probe? It's right next to the left anterior descending artery," he says. In July 2002 ("Mt. Olympus Goes Techie"), Zenati, professor of surgery and bioengineering, worked behind the controls of "Zeus," a robot designed to eliminate hand tremors while operating on the heart. Since then, Zenati has realized the limitations of anthropomorphic robots and teamed up with Carnegie Mellon University's Robotics Institute to develop cardiac robots that look more like snakes than human hands. Preclinical trials on pig hearts are confirming Zenati's predictions. His two newest bots, the Heartlander and Cardio ARM, can reach inside hearts at less invasive angles than previous robots, eliminating the need to deflate a patient's lungs. Cardiorobotics, the Pitt/CMU spin-off developing the technology, raised $11.6 million this summer. *—BE*

Boy meets Girl

Many of the stories in this magazine are, at heart, love stories. If you're going to try to bring about meaningful advances in medicine, passion and devotion seem to help.

Joseph Glorioso, for one, became smitten with the idea of gene therapy in the '90s, when he realized the virus he'd spent much of his career studying was probably the ideal vehicle for delivering therapeutic genes to the nervous system. Most of us would regard HSV1—the herpes simplex virus often associated with cold sores—as an irritant or worse. For Glorioso's purposes, herpes has it all: It naturally travels through neurons, where it excels in settling in and doing nothing.

Glorioso's lab has figured out a way to get it to deliver customized genes on demand while making the virus unable to replicate in the host (actually, most of us have HSV1 in our systems already).

"We've tried very hard to cause disease with these [engineered] organisms, and we just can't do it," Glorioso, professor of microbiology and molecular genetics, says with a chuckle.

There's a slight note of exasperation in his voice, as well. It's been an up-and-down ride for gene therapy devotees. As we reported in a July 2000 article ("Precious Cargo"), questions of safety arose 10 years ago after the death of Jesse Gelsinger, a young man enrolled in a trial at the University of Pennsylvania. Later gene therapy trials in France and elsewhere for severe combined immune deficiency, a.k.a. "boy in the bubble" disease, ended immunodeficiency for 19 of 20 children. But five patients contracted a leukemia-like cancer as a result of the therapy, from which one died. "Four are in remission with immunity still corrected by gene therapy," says Glorioso.

Ever faithful, in the past decade, Glorioso has built a strong gene therapy research program at Pitt with several independent investigators pursuing almost $16 million worth of studies in a wide range of diseases. At the moment, he is most excited about a treatment for chronic pain he developed that's now in a safety trial at the University of Michigan.

"In chronic pain syndrome, even touching the skin hurts," he says. "So these neurons start firing pain signals inappropriately. This kind of pain is a disease. ... People can't go to work; their lives are miserable. Long term, there's no treatment."

Unlike users of narcotics, patients don't build tolerance to Glorioso's treatment. Doctors inject the therapy at the site of the pain, then as Glorioso puts it, "there's this very cool thing that happens." A molecular motor in the nerve carries the virus up the length of the neuron. When it gets to the nucleus, the virus injects its DNA. The viral DNA is then entirely silent except for one gene built to release enkephalin, a naturally occurring substance in our bodies that binds to opioid receptors and relieves pain. The therapy blocks only chronic types of pain—not pangs that might signal a need to remove a hand from a flame, for example.

The biggest issue Glorioso foresees now: cost.

"NIH really doesn't have the money to move these therapies forward." So Glorioso has partnered with a local subsidiary of the Swedish firm Diamyd Medical. Moving forward to the next two clinical trial stages will run "probably $12 million." Yet his commitment is unwavering.

For treating nervous system conditions, he says in a hushed voice, "I think the system we're using is perfect." *—EL*

the Odyssey

It took Odysseus a decade to wend his way home after the fall of Troy. Perhaps he could have used a better navigator.

For some 30 years, Peter Strick has been helping researchers navigate on one of science's great journeys of discovery, the study of the brain. Strick, a PhD who codirects the Center for the Neural Basis of Cognition and is a Pitt professor of neurobiology and psychiatry, maps the circuitry of the brain.

Before Strick published a seminal paper on the topic in 1986, conventional thought had it that discrete areas of the brain performed discrete functions. This part controls thought. This part controls motion. This part controls speech. And so on.

Strick has long been involved in the study of Parkinson's and Huntington's diseases—which are based in the basal ganglia, a group of structures interconnected with the cerebral cortex and thalamus and associated with a variety of functions, including motor control, cognition, emotion, and learning. The basal ganglia were thought merely a locus of motor control before Strick came along. "Parkinson's and Huntington's are very different in terms of symptoms," Strick says, "but they affect different portions of the same neural structure."

This elemental understanding has forced scientists to rethink treatments for neurological disorders. The standard treatment for Parkinson's has been to prescribe L-dopa—a drug used to replace the neurotransmitter dopamine. But today, a neurosurgeon might implant electrodes in the particular neural loop related to the symptoms, a procedure called deep brain stimulation.

The thinking that led to this treatment, Strick says, represents the biggest shift in the past decade of neuroscience. "We now understand that disorders are specific to [brain] systems [rather than just structures], and that the treatment has to be focused to deal with the pathophysiology."

We first wrote about Strick's work in our July 2002 cover story, "The Sweet Science of Movement." Within the past year, the scientist has helped explain why a musician may have the dexterity to, say, play the lyre as adeptly as one of Homer's Sirens. In many animals, the primary motor cortex controls movement through the circuitry of the spinal cord. But "higher" primates, like humans, evolved an area of the cortex that communicates directly with specific spinal cord motor neurons, which instruct shoulder, elbow, and finger muscles to perform. This direct connection, Strick says, accounts for added deftness with small, specific movements.

Karl Kandler is another Pitt researcher erecting key guideposts to help us find our way around the brain. He specializes in the circuits that tell the brain when to go fast and when to lay off the accelerator.

Inhibitory neural pathways, says Kandler, act like a governor on a car engine. The brain may be capable of going as fast as a Ferrari, but it shouldn't; unrestrained neural activity can be the cause of seizures and has been related to schizophrenia.

Kandler, a PhD associate professor of otolaryngology and neurobiology at Pitt, studies the auditory brain system, where many of the pathways are purely inhibitory and well defined. Kandler chose this system for study about 10 years ago, and in October 2002, *Pitt Med* reported ("The Brakes of the Brain") on his early progress that landed him national attention, notably a Presidential Early Career Award for Scientists and Engineers.

Prior to 2005, Kandler reports, it was thought that excitatory neurons—which stimulate cells to act—only released excitatory neurotransmitters such as glutamate and inhibitory transmitters only released inhibitory neurotransmitters like GABA and glycine.

During the past couple of years, however, Kandler has found that in young rats, developing inhibitory neurons in the auditory brain system release glutamate.

More recently still, Kandler discovered that the production of glutamate is vital for the proper development of inhibitory neurons. Mice engineered so they are unable to produce the neurotransmitter, he says, experienced nonconvulsive seizures, indicating that the "brakes of the brain" were not working properly, that the excitatory circuits were overloaded.

If things pan out the same way in humans, says Kandler, it may be possible to use this mouse-derived knowledge to develop drugs to restore the brakes to good condition in people with disorders such as schizophrenia, epilepsy, and tinnitus. —*JM*

Getting into med school can be an epic quest in and of itself. But imagine finally arriving at the school you chose—and that, thank the gods of Mt. Olympus, chose you—only to find out that getting your MD from this particular university would be more complicated than you'd thought.

Sheena Jain (MD '08) recalls feeling a bit anxious at orientation five years ago when she learned about a brand-new curriculum requirement: the scholarly research project. But the project turned out to be a blessing in disguise.

The faculty explained that day at orientation that each student would pair with a mentor who guides her in designing a scientific-research project. As this magazine has reported on a number of occasions, typically the project is a long-term, in-depth study that begins the fall of the second year.

The 270 projects completed thus far have run the gamut, focusing on everything from necrotizing enterocolitis in premature infants to the role of life experience in shaping attitudes in end-of-life care. One student even wrote a medically based mystery/thriller novel.

Working with her mentor, radiation oncologist Sushil Beriwal, Jain did a retrospective, comparative study of clinical outcomes for endometrial-cancer patients who underwent different radiation therapies. Based on the strength of her project, she was asked to represent Pitt at the 2007 Annual Meeting of the Association of American Medical Colleges. Along with two other classmates, Jain answered questions in the exhibit area for conference attendees, many of whom were curious about Pitt's new curriculum, which won an AAMC award for innovation in preclinical education.

Pitt's scholarly research project requirement is designed to give students a preview of the world of academic medicine. It's also designed to create leaders in medicine who can absorb research



Karl Kandler (the tall one) grew up closely observing animal behavior. Now he's the expert on the "brakes of the brain." He's shown here at home in a 2002 photo.

advances, whether or not they have any interest in pursuing a vocation steeped in grants and data.

"This was great for me as a clinician," Jain says of the project. "New research articles are published every day, and you're always going to find contradictory information. I think the only way to gain that appreciation and learn how to read critically is by actually *doing* research."

An added bonus: The scholarly project has also made the dreaded odyssey that is The Job Hunt a little less tortuous. "By far what I was asked about most in interviews was my research," Jain says as she wraps up her last two weeks as a UPMC intern—after that, she's bound for a radiation oncology position at the University of Texas Southwestern Medical Center at Dallas. "If I didn't have that on my resume, I don't know what we would've talked about. Overall, from talking with my classmates, I think our research projects made us much more competitive. We have a real advantage." —*EV*

Coming of Age



Preliminary data from the National Institutes of Health place Pitt and its affiliates fifth among institutions receiving the agency's support.

In 1998, when he took the helm as Pitt's senior vice chancellor for the health sciences and dean of the medical school, Arthur S. Levine had three main goals: Ramp up basic science research, continue the tradition of clinical excellence at the teaching hospitals, and attract some of the best med students in the country.

Done, done, and done.

We reported in 2000 ("His Aim is True") how Levine, an MD, came from the National Institutes of Health (NIH) to fill the rather large shoes of his predecessor, Thomas Detre. Beginning with his leadership of Western Psychiatric Institute and Clinic in the 1970s and later as senior vice chancellor for health sciences, Detre helped transform Pitt from a regional med school best known as the birthplace of the polio vaccine into an up-and-coming national brand.

Under Detre, Pitt's modern academic medical center was born and learned to walk and play with the big kids. Under Levine, it has matured and gotten into poetry, art, home improvement, and marathons. Older and wiser, sure. But slowing down? Don't bet on it.

That's probably a good thing for Pittsburgh. Last year the University brought in about $642 million in outside funding for research and other programs, supporting more than 23,000 jobs; much of the funding relates to biomedical work. The biomedical enterprise that has sprouted around Pitt and UPMC has helped the city weather the country's worst financial crisis since the Great Depression.

In addition to its federal and philanthropic support, the medical school's symbiotic relationship with UPMC, the region's largest employer, has helped it blossom. The teaching hospitals rely on Pitt faculty to deliver care; UPMC in turn invests profits ($146.6 million in 2008) from patient care into research and education. UPMC supports the training of residents and fellows, who are UPMC employees. Other Pitt health sciences schools receive funds, as well.

With the school in a position of strength, Levine created several new departments in the clinical and basic sciences. Two of these—structural biology and computational biology—are now housed in Biomedical Science Tower 3, a $205 million high-tech hive opened in 2005. Levine recruited Angela Gronenborn, a decorated scientist at the NIH, to help design the building and become the UPMC Rosalind Franklin Professor and inaugural chair of structural biology. "I could see the chance for this cross-fertilization of physicians and basic researchers to learn each others' language and push their way forward," says Gronenborn, who was inducted into the National Academy of Sciences in 2007.

The med school has established an Academy of Master Educators to recognize outstanding instructors and steadily shaped its curriculum with the changing nature of medicine. It now requires students to complete a scholarly research project. And fourth-years revisit basic science material after the whirl of third-year clinical rotations. "After you've seen patients with leukemia, it's really good to be able to go back and revisit the science underlying leukemia to tie everything together," says Steven Kanter, vice dean.

Levine has invested in scholarship money to lure top med school students, who now bypass the likes of Stanford, Johns Hopkins, and the Ivies to come to Cardiac Hill. "One of my goals coming in has been to attract a different kind of student—students who would be leaders in their profession," Levine says.

Still, these are daunting economic times, and the future of academic medical centers like Pitt depends on factors that no one, not even Art Levine, can control. Health care reform, in whatever shape it comes, could reduce compensation. More alignment with industry will be necessary, Levine says. But the need should be tempered by policies that keep the medical mission and revenue motive separate, he says. Pitt has already put a lot of thought into how to reduce inappropriate influence (see our Spring 2008 cover story, "A New Diet for Docs"). The American Medical Student Association gave Pitt's efforts very high marks in both 2008 and 2009.

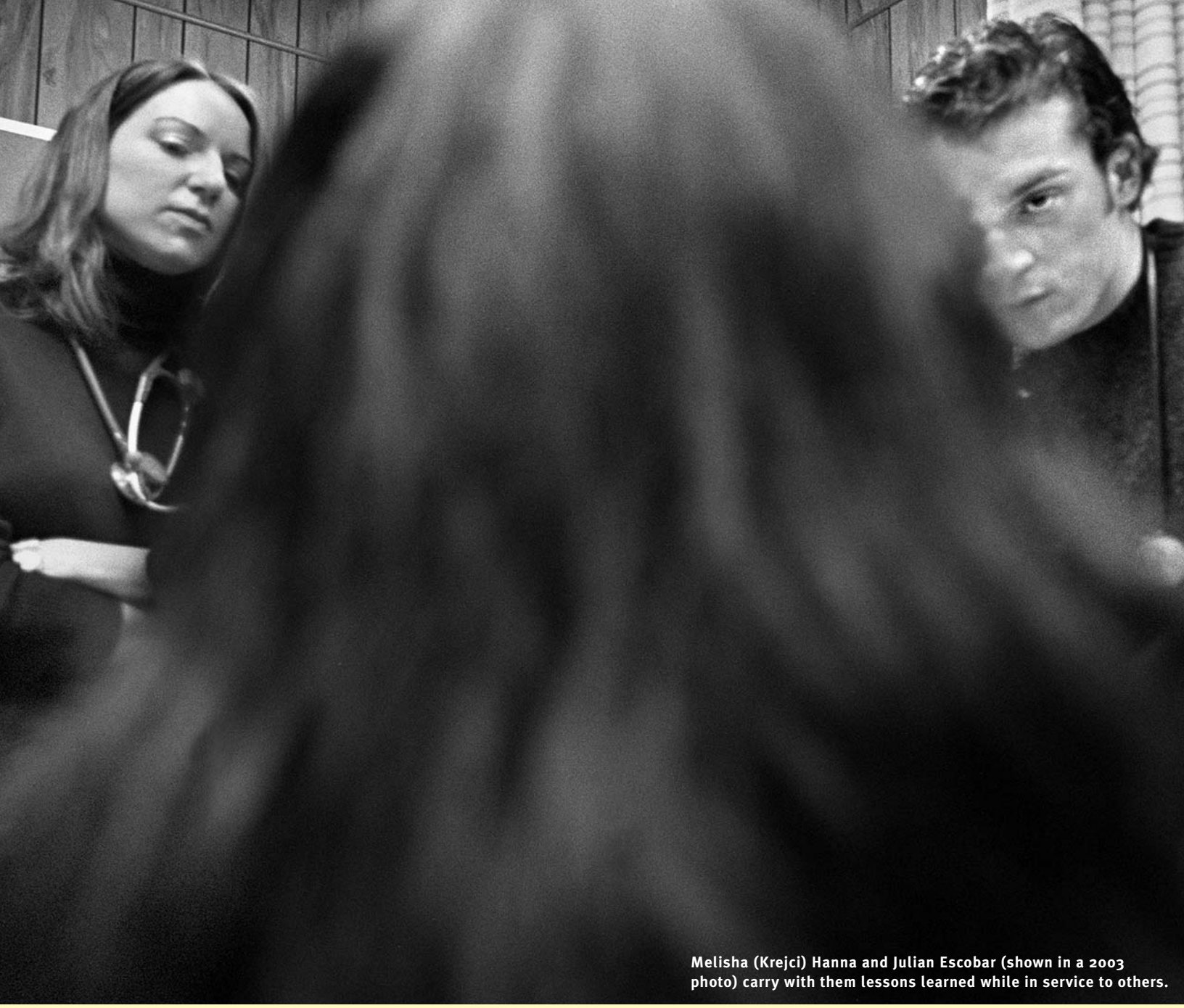
Regardless of the uncertainties, this is no time to wind down on academic medicine, Levine argues: "To prevent a disease, you have to know what's causing it. We can't let up on our support for research."

The academic medical center has grown up. Now, perhaps, comes the hardest part. —*Reid R. Frazier*

The great coming of age stories all function on the mechanics of a simple equation: At some point in our lives, we see things that make us unpack the valise of received knowledge we've carried around up until that point. Huckleberry Finn's eye-opening experience came while sharing a raft on the Mississippi River with an escaped slave named Jim. Holden Caulfield's came on a weekend alone in New York City.

For some Pitt med students, the *bildungsroman* moment comes while serving those in need. In May 2003 ("Modern Day Schweitzers"), we reported on the whirlwind of activity behind Julian Escobar and Melisha (Krejci) Hanna (both MD '04) cofounding Students and Latinos United against Disparities (SALUD), a health service for Pittsburgh's small but growing Latino population. Escobar and Hanna put SALUD together with help from a U.S. Schweitzer Fellowship.

Escobar, who'd grown up in Bogotá and came to Dallas in the early 1990s as a teenager, never considered himself "Latino" before



Melisha (Krejci) Hanna and Julian Escobar (shown in a 2003 photo) carry with them lessons learned while in service to others.

med school. That began to change while working on SALUD, which Pitt med students continue to run. (With a dozen fellows this year, the Schweitzer program remains strong at Pitt, as well.)

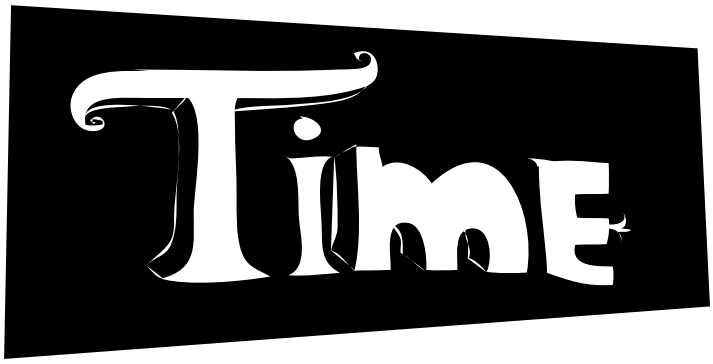
One day in 2003, Escobar was looking for a Spanish translation of the HIPAA statement. He called a hospital office to see whether there were any on hand. "We only have those forms in *American*," Escobar remembers the woman on the other end saying.

"I knew right then that I had this responsibility to educate people around me. I knew I wanted to help the Latino community help itself," he says.

Escobar went on to an ob/gyn residency at Northwestern University. He's now a fellow in reproductive endocrinology and infertility at the University of Texas Southwestern Medical Center at Dallas. His clinic is one of the few of its kind that accepts Medicaid patients, a point of special emphasis for Escobar. "Just because you're poor, or don't speak English, that doesn't mean you shouldn't have access to this care," Escobar says.

Hanna is now at Children's Memorial Hospital in Chicago, where she's completing a pediatric nephrology fellowship and working on a project to improve hypertension screening and care for adolescents from disadvantaged backgrounds.

A long list of Pitt med alums we've chronicled have continued on the path illuminated by their coming-of-age experience. Kate Dickman (MD '09), for example, spent two years in Uganda conducting research on tuberculosis as a Fogarty International Clinical Research Scholar ("Breaking Ground," Fall 2007). She's now in the Boston Combined Residency Program in Pediatrics, run through Harvard and Boston universities. After residency, she'll likely look for a postdoc in public health. At Pitt, she became interested in working with children while volunteering at a pediatric malaria clinic in rural Kenya. Watching children die of a preventable and treatable disease gave her direction and a purpose. "You see something horrific," she says, "and you want to try to make it better." *—RRF*



Authors have long used time as a device in their plots. You could practically hear the clock ticking as we shadowed Brian Pettiford (MD '96, Res '01, Fel '03) during his cardiac surgery fellowship ("On the Clock," October 2002). There were plenty of opportunities for him to wield a scalpel during those 110-hour workweeks, yet scant sleep and foregone family time were part of the price of a now-defunct approach to medical training. Looking back, Pettiford, a Pitt faculty member who will join a private cardiology practice in York, Pa., this fall, says, "If it doesn't kill you, it makes you better."

Not everyone agreed that lives lived in defiance of time was the best situation. An Accreditation Council for Graduate Medical Education standard barring trainees from working more than 80 hours a week—averaged over a month—or shifts longer than 24 hours went into effect on July 1, 2003. Amid growing concern about the effects of fatigue on both patient care and house-staff health, Pitt adopted the standard a year ahead of the national deadline. (Pettiford completed about 90 percent of his training under the old rules.)

The transformation has been profound, says Rita Patel, associate dean for graduate medical education: "It focuses you on the most important things for residents to learn." Today, simulations, podcasts, and online programs guarantee exposure to the unusual cases a resident previously encountered only if she happened to be present when such a patient arrived. Fatigue-recognition training cultivates a shared responsibility for physician health.

The medical center now focuses on strategies for effective patient transfer and team communication. "You're altering the whole culture, moving from a hero-based system—where if you're a patient you hope you hit the right person who can get you out alive—to systemic structures [that] carry you through in a reliable fashion," says Dennis Zerega, vice president for graduate medical education. "It moves from individual heroics to system predictability." *—Sharon Tregaskis*

Why do we age? In a February 2005 headline, *Pitt Med* posed that grammatically simple yet scientifically complex question. Laura Niedernhofer, a Pitt associate professor of microbiology and molecular genetics, proposed that rather than a single underlying mechanism controlling aging throughout the body, aging was probably the result of the gradual accumulation of random damage to cells and molecules. Eventually, the body can't keep up with the necessary repairs.

In the field of aging research, this view has won out, says Niedernhofer, adding, "We are fortunate enough to have the research community embrace our model as one of aging, and we are using it to look for those sorts of 'magic treatments' that might help us live longer and healthier."

The model she refers to is a strain of genetically modified mice deficient in repairing what are known as the interstrand crosslinks of DNA. The mice seem to age in fast-forward, she says, implicating crosslinks in natural aging.

Niedernhofer now works with at least 10 different collaborating labs across Pitt's campus that use her models.

The extent of such collaborations, she says, underscores the growing strength of Pitt as a place for research into aging and DNA repair. Several dozen med school faculty list one or both of these areas among their research interests, including (and this is not a coincidence) Arthur S. Levine, dean of the school and senior vice chancellor for the health sciences.

"I can't think of a better place" to do this work, says Niedernhofer. *—CS*

When the AIDS epidemic first emerged some 30 years ago, it presented the face of a ghoul. Doctors gowned up when seeing patients, even though they knew its pathogen was not airborne.

With the passage of time, the wonder of antiretroviral drugs, and our immense capacity to forget, the old specter has passed, and we now see in its place something totally different—a chronic disease that, many assume, we can live with. That's a dangerous attitude. More than 33 million people now are infected with HIV, two-thirds of them in sub-Saharan Africa. The number of new infections—in the United States, as well—keeps rising. And drug-resistant strains have emerged.

This makes the task before researchers all the more urgent. As we reported in 2002 ("The Virus Keeps Hiding"), Charles Rinaldo, chair and professor of infectious diseases and microbiology in the Graduate School of Public Health and professor of pathology in the School of Medicine, started tracking the health of gay men in Pittsburgh in 1984. The study remains a gold mine for AIDS researchers. Rinaldo's group now focuses on AIDS in its midlife as a pandemic—studying the long-term effects of AIDS drugs and the relationship between HIV and cancer.

It was with samples from Rinaldo's study that John Mellors, chief of the Division of Infectious Diseases and director of UPMC's HIV/AIDS Program, discovered one of the field's best diagnostics—the viral load test.

An HIV vaccine has proved elusive, so Mellors, like many researchers, is focused on prevention. He's looking for new antiretrovirals to treat and prevent HIV-1 infection.

AIDS researchers now face a foe perhaps bigger than the disease itself: the notion that we have the luxury of time to deal with this killer. *—RRF*



Peter Safar's arena was where human lives teeter on the edge.

Death

For a time, Peter Safar cheated death, as we noted in the first issue of this magazine ("Time of Death: Postponed," October 1999). One could make the argument that he cheats it still. His life's work was resuscitation, and his arena was where human lives teeter on the edge—the accident scene, the battlefield, the ambulance, the operating theater, and intensive care. He was a Pitt Distinguished Service Professor and founder of its critical care medicine program. In the wider world, he was hailed as "the father of CPR." To his colleagues at the University of Pittsburgh, he was a dear friend and a mentor without peer.

Safar died in 2003 at age 79, but his legacy thrives. A cadre of Pitt scientists and physicians have carried his research forward. Now his CPR legacy may soon be eclipsed by one of therapeutic hypothermia—chilling patients to save their brain function and their lives.

In 2003, the American Heart Association recommended mild hypothermia for ventricular fibrillation cardiac arrest. Many medical centers have yet to adapt, but Pitt-affiliated hospitals now use hypothermia in about 85 percent of eligible cardiac arrest cases. The data show clear benefit in brain function after recovery. The data are even stronger for the use of hypothermia in newborns with birth asphyxia. All of this stems from decades of hypothermia research conducted at Pitt.

Mild hypothermia is exciting, but deep hypothermia seems downright futuristic. Imagine a high-speed collision in which a person suffers trauma to the chest. Paramedics administer blood and saline, but everything simply leaks out of a tear in the pulmonary artery. Blood pressure plummets, and cardiac arrest ensues. Any trauma surgeon can tell you that this is a lost cause; there simply isn't enough time. To slow the clock, associate professor of surgery and critical care medicine Samuel Tisherman (MD '85, Res '93, Fel '91 & '94) is proceeding with the first clinical trial of emergency preservation and resuscitation (EPR).

Medical personnel will deliver an ice-cold flush of saline through the aorta. It will course through the circulatory system. It will leak out in this case, too—but that doesn't matter, because the patient will be chilled to below 60 degrees Fahrenheit in less than 20 minutes. He'll be left with no heartbeat and no brain activity. A surgeon will repair the injury while the patient has no pulse. Theoretically, this could go on as long as an hour or two. You can bet, however, that the surgeons will try to finish the procedure in closer to 30 minutes. Despite the reams of laboratory evidence and anecdotal "fell through the ice and survived" stories suggesting this will work, nobody likes a patient without a pulse.

Then doctors will gradually rewarm the patient with fluids and the heart should start beating again. Safar himself, who worked to make EPR happen, reportedly described it to a visitor to his laboratory this way:

"He's dead now, but he'll be fine in a few hours." *—CS*



Half the Ethiopian population was said to live more than a two-day walk from any accessible road. "Accessible" was generously defined

TARGET ZERO

SMALLPOX— THE DEATH OF A DISEASE

BY D.A. HENDERSON

On October 26, 1966, D.A. Henderson reported at Geneva headquarters to lead a global war. The enemy, embedded with civilians on three different continents, refused to negotiate. In the last 100 years of its existence, smallpox had killed at least half a billion people. After infecting its hosts, the disease caused high fever, severe aching pains, and rash. Pressurized pustules eventually poked through the face of the afflicted like buckshot, and once the pustules merged into sheets, the host was likely to die.

The mission objective, code-named "Target Zero," was simple—eradicate smallpox from the human population in 10 years. The means were more complicated. Early estimates required between 200 to 350 million vaccinations every year for the next 10 years, at a total cost of at least $180 million. Many, including World Health Organization Director-General Marcelino Candau, thought the chance of success was slim. The WHO was financing a failing malaria eradication program, and, according to Henderson, Candau was distressed about growing criticism of his organization. He decided an American should direct the U.S.–backed program. Thus, when the program failed, the United States would share the blame. He selected Henderson and gave him only $2.4 million a year. A little more than 10 years later, the last smallpox case occurred in Somalia.

Henderson, a professor of medicine and public health at the University of Pittsburgh and a resident scholar at the Center for Biosecurity of UPMC, released his book Smallpox—The Death of a Disease *(Prometheus Books) in June. The following excerpts give a glimpse of how Henderson's team killed a 3,000-year-old disease. (Reprinted with permission, © 2009, D.A. Henderson.)* —Brandon Ellis

THE FUTILITY OF ERADICATION

The widely read and respected medical scientist Dr. René Dubos took a dim view of the concept of eradication and wrote about it in 1965 in his book *Man Adapting*. It was a view that was widely shared at the time. However, by the time I got around to reading the book, my future had already been decided.

Dubos wrote: "At first sight, the decision to eradicate certain microbial diseases appears to constitute but one more step forward in the development of the control policies initiated by the great sanitarians of the nineteenth century. ... In reality, however, eradication involves a new biological philosophy. ... Social considerations make it probably useless to discuss the theoretical flaws and technical difficulties of eradication programs, because more earthly factors will certainly bring them soon to a gentle and silent death. Eradication programs will eventually become a curiosity item on library shelves, just as have all social utopias."

WHY WE BELIEVED SMALLPOX COULD BE ERADICATED

Smallpox and the freeze-dried smallpox vaccine possessed unusual characteristics. Taken together, they were unique and made smallpox, by far, the best available candidate disease for eradication. Most important, humans were the only victims of the smallpox virus; and there was no reservoir in nature. No rodents, monkeys, or other animals could be infected. Each person who was infected exhibited a rash that could be identified even by illiterate villagers. No laboratory tests were required. If patients were promptly isolated, they could be prevented from spreading infection. Moreover, a patient could infect others only during the two to three weeks of severe illness; on recovery, the person was immune for life.

The development of freeze-dried vaccine was a critical advance. It could withstand storage at 98°F (37°C) for a month, making it ideal for tropical areas. The vaccine was inexpensive, vaccination was easily performed, and a single vaccination provided immunity for at least 10 years. Every successful vaccination resulted in a pustule and then a distinctive scar, which remained for decades. In areas where *Variola major* has been the prevalent form of smallpox, 80 percent of those who recovered had permanent scars. Thus, teams visiting an area could readily determine whether smallpox was present in the community, when it had occurred in the past, and who had been successfully vaccinated. No other disease came close to being such an ideal target.

INDIA

The commitment and determination of the Indian Central Appraisal Team staff was as extraordinary as its accomplishments. At the January 1, 1974, strategy meeting of the team, it was apparent to me that they were all exhausted and some were near the point of collapse. All had been working seven-day weeks for four months. They had repeatedly made difficult trips throughout some of the country's most remote and inhospitable areas in a frantic effort to motivate the army of health workers to contain outbreaks. Four of the members had serious medical problems. One had incapacitating renal colic; one had painful facial herpes; another had a serious fungus infection, which eventually required surgery; and one had atypical pneumonia with a high fever and pleuritic pain. However, the

only problem they would discuss was where to find the additional resources to keep the program going. I expressed skepticism about their own ability to keep up with the grueling schedule even if resources could be found. Bill Foege replied simply: "We've considered the question and have decided that things can't get worse; therefore they must get better."

Some of the [team's] expenditures were out of the ordinary, and special justifications were needed. There are several that I remember well. One was a receipt for costs associated



A thornbush barrier quarantines a nomad in East Africa.

with rental of elephants—to ford rivers and, later, for public advertising of a reward for reporting a case. Food costs to feed beggar families in infected compounds—so that family members would not go out begging. Purchase of the body of a deceased smallpox case for burial—otherwise it would have been floated down the Ganges.

ETHIOPIA

There are few places that rival the sheer beauty of mountainous Ethiopia—as well as few places where, day to day, the staff encountered more potentially threatening personal hazards and perils.

One adventure involved running out of gas over the Blue Nile Gorge in a single-wing two-passenger plane. The plane had been leased to permit me to meet with staff some two hours away from Addis [Ababa]. On the return flight, the motor sputtered and died. We were directly over the gorge—5,000 feet above the Blue Nile—at least a mile from the edge of the canyon. The pilot was a distressingly casual Swede who mentioned that he had forgotten to put on the gas cap. The gasoline had drained out. He switched to the second tank and eventually managed to get the engine restarted. As we approached the Addis airport, the engine again began to sputter, and the pilot called the airport to announce an emergency landing. However, a passenger jet was descending at the time. The tower and the two pilots engaged in a heated argument before the jet finally pulled up. As we began to taxi, our plane's engine stopped altogether. Two months later the Swedish pilot was killed and the plane crashed when a large buzzard penetrated the cockpit window and impaled itself in the pilot's chest.

SOMALIA

In 1977, Somalia declared the smallpox epidemic a disaster and the United Nations Disaster Relief Operations agreed. Eradication workers responded from all over the world to close in on the last known cases. They were determined to finish the job before the annual Haj pilgrimage to Mecca, which would take place in November that year and threatened to set off another wave of infection worldwide.

The number of cases rose to 1,388 in June and the number of infected villages to 223. Containing the outbreaks, especially among the nomad populations, proved to be a challenge quite unlike any faced before. The proportion of outbreaks among nomads rose from 50 percent in April to 75 percent in June and more than 90 percent in July.

The nomads typically began their most active migrations in March when the rainy season began. They tended not to follow established patterns of movement but to seek good grazing for their animals wherever that might take them. Their vaccination levels, wherever checked, were usually in the range of 10 to 20 percent. Simply finding the nomads in the scrub desert was an adventure. Line-of-sight vision was blocked in every direction by the high scrub. No maps were available and few landmarks existed. The only good lead was the knowledge that the nomads must find water holes. In some areas, lookouts were posted at every water hole to keep a vigil for the nomads.

The smallpox-affected localities steadily diminished in number … to only 29 in September. But then torrential rains hampered the use of heavy vehicles. Many field staff were obliged to travel on foot or on camels and donkeys. On October 31, 1977, a final case was discovered in the port town of Merca.

Ali Maow Maalin was a 23-year-old cook at the local hospital. He developed a fever on October 22, followed by a rash on October 26. His case was a classic one in depicting omissions and mistakes in program operations. He had never been vaccinated, despite having once served as a vaccinator and despite having worked at the hospital where employee vaccinations were supposed to be mandatory. On October 12, two sick children arrived at the hospital in a vehicle from a nomad encampment. They were to be housed in an isolation camp nearby. Both of them had smallpox, and one died two days later. Maalin volunteered to ride with them to direct the driver to the camp about 200 yards away. His exposure was brief but adequate.

Maalin was admitted to the hospital on October 25 with a presumptive diagnosis of malaria. He received numerous visitors and walked freely around the hospital and outside the compound. A day later he developed a rash that was diagnosed as chicken pox, and he was sent home. A popular man, he received many visitors until October 30 when a nurse suspected that Maalin had smallpox. He was then sent immediately to the isolation camp.

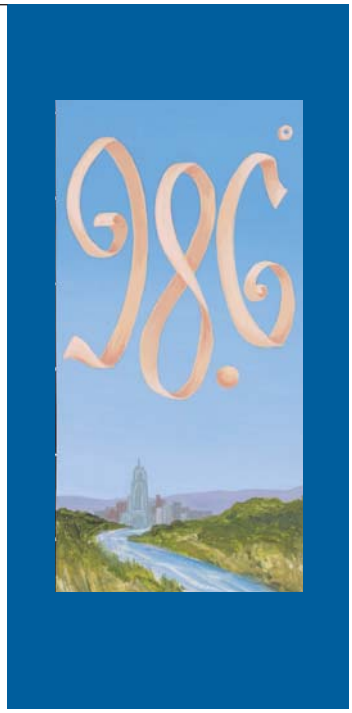
An intensive search began to find everyone with whom he had come into contact. In all, 91 face-to-face contacts were identified, 12 of whom had no vaccination scar, and six who had been hospital patients or visitors. Heroic measures were taken, including a search and vaccination of the town and of everyone entering or leaving town at any one of four checkpoints. House-by-house searches throughout the region were conducted monthly, and a national search was completed on December 29.

The epidemic was stopped before the annual pilgrimage to Mecca got under way.

Ali Maow Maalin survived his illness and continued to reside in Merca. He has a place in history as the last naturally occurring case in a continuing chain of transmission extending back at least 3,500 years.

Henderson ends his book with a warning: Smallpox may have been eliminated from the human population, but it still lurks. After the eradication, WHO sanctioned two national laboratories to hold frozen samples of smallpox, one in Atlanta and one in Moscow. When the Soviet Union collapsed, defectors revealed that smallpox had been the crown jewel of the Soviet bioweapons program. Some scientists who left the program have been impossible to track down. No one knows whether some smallpox samples might have moved into ill-meaning hands; and the organism could spread "more readily than ever," Henderson says, in an unprotected world population. Henderson worked with the Centers for Disease Control and Prevention to develop more than 200 million doses of smallpox vaccine after the attacks of September 11, 2001. However, he remains concerned even now about the possible return of his nemesis. —BE

People and programs that keep the school healthy and vibrant





GABRIEL SILVERMAN

The Class of '09 ran an inspiring fundraising campaign.

THEY RAISED HOW MUCH?

THE CLASS OF '09 LEADS THE WAY

BY BRANDON ELLIS

Lauren Toney remembers the moment it began. Sitting on the cusp of their medical careers in 2005, Toney (MD '09) and other first-year med students were relaxing in the lobby of Scaife Hall. Four daunting years of medical education awaited them, but they weren't worried. They were discussing how they could leave a mark here in Pittsburgh—one that would stand apart from their individual academic achievements and reflect the best of their intentions upon entering the medical profession. They decided to start a charitable giving project, and the name they came up with decided the rest: "90K from 2009." It was a concise, bold assertion that they would raise $90,000 before they graduated.

Toney, who cochaired the campaign, had done some fundraising in high school, and it seemed simple enough to her. But she didn't foresee a Saturday afternoon in uniform behind a counter, taking orders for nachos, pizzas, and sub sandwiches from the hoarse utterances emanating from black-and-gold painted faces. Working concessions at Steelers and Pirates games was one of the many ways that students raised money. The students also wrote letters to friends and faculty members encouraging them to give, sang karaoke at a pub, and hosted a mixer in the Strip District attended by graduate students from all of Pittsburgh's universities (raising $5,000 from that event). Toney knew the entire School of Medicine was behind the effort when students from other classes asked if they could help.

By May's graduation weekend, the Class of 2009 had raised more than $63,000, all of which would be donated to the Program for Healthcare to Underserved Population's Birmingham Free Clinic on Pittsburgh's South Side. The clinic treats uninsured patients. According to clinic director Mary Herbert, the money couldn't come at a better time. Complete with four private patient rooms, a new clinic opened in December 2008 with support from its community partner, the Salvation Army. The previous clinic had only two patient "rooms" separated by a curtain. To complement the physical expansion, Herbert wants to use the donated funds—the largest single donation in the program's history—to buy diagnostic equipment like EKG and ultrasound machines.

The class intends to raise the rest of the $90,000 for the clinic.

The Birmingham Free Clinic was an easy choice, according to the newly minted MDs. Most med students volunteer at the clinic at some point during their four years at Pitt. The clinic's patients are among the first real patients with whom students are able to interact. They give students the gift of allowing them to glimpse their futures as medical professionals. To the Class of '09, it is a gift exchange in which they are glad to take part. ■

BOOSTER SHOTS

The Class of '55 has stepped up its drive to elevate its class scholarship fund to new heights. **Robert Potter** (MD '55) is determined to help. Together with his wife, **Janet Potter**, the retired general practitioner has made a $50,000 planned gift to the fund. This follows on the heels of a $20,000 charitable gift annuity the Potters set up in 2008. (The couple received a charitable tax deduction based on the value of the gift, and a portion of their annual income from the annuity is tax-free.) Potter worked evenings and summers at U.S. Steel during med school, so he was able to graduate debt-free. Students today graduate with an average debt of $130,000. At recent alumni functions, Potter has been impressed with the intelligence, creativity, and academic achievements of today's Pitt med students. He hopes that gifts like his will make it easier for these aspiring physicians to excel.

Virginia Kaufman made her way to Pittsburgh in the late 1930s as a recent graduate of Clarion State Teachers College, in Clarion, Pa. She valued her education but did not want to teach. Kaufman found work in advertising and market research, eventually becoming a partner in Penn-Art Associates, which provided graphic design and marketing services to major corporations for more than 50 years. Upon her death in 2008, her estate made a planned gift of $1.8 million to the School of Medicine to support work in the area of pain management. —*CS*

FOR INFORMATION ON GIVING TO THE SCHOOL:
Deb Desjardins, 412-647-3792, ddeb@pmhsf.org



CLASS NOTES

'60s

Bob Kunkel (MD '60) has never had a headache in his life, but he knows how to treat every kind. As a first-year physician at the Cleveland Clinic, Kunkel worked under a senior physician who listened to patient headache complaints when most other doctors ignored them. Kunkel saw how patients appreciated him for taking them seriously and relieving their pain and thus found his own specialty. In the 1970s, he established a headache center at the Cleveland Clinic, where he has since treated everything from brain-searing cluster headaches to recurring migraines. He was president of the American Association for the Study of Headache from 1980 to 1982, and served as the U.S. representative on the steering committee for the International Headache Society. After almost 50 years of crafting the study of headache into a serious specialty, Kunkel is now retired, but he still can't escape his area of expertise. He is a volunteer in a study comparing headache sufferers to non-sufferers. He's also updating his handbook on headaches that was first published in 2007.

'70s

When **Ronald David** (Pediatrics Resident '78) tries to explain to his daughter why he moved from hospital administration to pastoral education, he calls himself "peripatetic." She retorts "very pathetic," and tells him he can never make up his mind. But for David, working with theological students at the Hospital of the Good Samaritan in Los Angeles is a logical next step in his varied career. He was chief resident at Children's Hospital of Pittsburgh. As a Pitt assistant professor of pediatrics, he cofounded a transitional infant care program at the Children's Home of Pittsburgh before moving into public health administration. He was acting deputy secretary of health for Pennsylvania under Governor Robert Casey. He joined the faculty of Harvard University's John F. Kennedy School of Government as a lecturer in public policy with a research interest in women's health. As chief medical officer for the District of Columbia's Health and Hospitals Public Benefit Corporation, he says that he witnessed much despair and dysfunction, as well as "moments of miracle and majesty." Spirituality is an essential but overlooked component of health, says David, who is now a certified clinical chaplain. He guides theological students in Los Angeles through their encounters with the sick and dying and is writing a book about the relationship between health, spirituality, and religion.

'80s

Peter Lambrou (Orthopaedic Surgery Resident '82) met the crew of US Airways Flight 1549 after it crash-landed in the Hudson River last January. The airline and pilots' association asked him to medically screen the crew before they spoke to the press. Lambrou knows the pressures involved in guiding jet planes through the sky. He's in his 23rd year with US Airways as a commercial pilot and has piloted transoceanic flights to Frankfurt and Madrid. The president and founder of the Center for Aviation Medicine near Pittsburgh, Lambrou helps pilots regain their licenses after losing them for medical reasons. As a pilot who cannot remember a time when he did not want to be a pilot, he says he understands why they want to be airborne again.

At Lahey Clinic in Massachusetts, **Anthony Gray** (MD '85) expands lungs, implants stents, drains fluids, and opens new airways to help patients breathe better. One of Gray's hardest jobs is easing the transition for a patient who won't survive lung disease. "At the same time, it is the one aspect of my job I wouldn't change for anything. It's an act of love that brings me closer to my patients." Patients at the outpatient pulmonary rehabilitation clinic, which he directs, are often severely limited by advanced lung disease. With intensive, supervised exercise and education, these patients often achieve significantly higher levels of functioning. In the mid-1990s, he and his mentor at Lahey started the first interventional pulmonary fellowship program, of which there are now 11 in the country.

'90s

On Mondays, **Peter Ubel** (Internal Medicine Fellow '94) gives his two sons 20 minutes each of screen time if they want it. But if they wait until Tuesday, dad gives 25 minutes. If they hold out until Friday, dad gives 40 minutes. "They have yet to make it to Friday," laments Ubel. He says that if his sons were rational creatures, according to Adam Smith's classic model of economics, they would wait until Friday. But they're not rational. None of us are. This is the central premise behind Ubel's latest book, *Free Market Madness* (Harvard Business Press, 2009), about the clash between the harmful choices we actually make compared to the rational choices capitalist theory presupposes we make. In medicine, this same capitalist philosophy supports the theory of patient autonomy, but Ubel argues that sometimes others need to make choices for us. Ubel is a professor of internal medicine at the University of Michigan, where he directs the Center for Behavioral and Decision Sciences in Medicine.

About to remove a tumor from the brain of a 3-day-old infant, **Paul Grabb** (Neurological Surgery Resident '95) suddenly stopped operating and blurted out a four-letter word: *Foot!* Inside Sam Esquibel's tiny skull was a foot and other partially





Peter Ubel (above). Paul Grabb (on the left) with a colleague in the OR.

formed appendages, which Grabb later diagnosed as a teratoma, a type of brain tumor composed of foreign tissue. He removed the benign tumor and baby Sam achieved a full recovery. After the local paper printed the story, it went viral. Grabb appeared on the *Today Show* and finally went skiing to escape the incessant media attention. A father of two teenage boys, Grabb says that his only thoughts during this procedure were of how he wanted the parents of Sam Esquibel to see their son grow up healthy and happy. Grabb is the director of pediatric neurosurgery at Memorial Hospital for Children in Colorado Springs, Colo.

Yvette Kasamon (MD '99) recalls the summers she fell in love with cancer immunology, when she worked in Walter Storkus' lab at Pitt. Then, the goal was developing vaccines for melanoma and renal cancer. Now, as a lymphoma expert and assistant professor of oncology and medicine at Johns Hopkins University, she develops and leads clinical trials for Hodgkin's and non-Hodgkin's lymphoma. Her recent trial used the results of positron emission tomography (PET) scans to adjust chemotherapy treatment for patients, a new approach for non-Hodgkin's lymphoma.

'00s

Her skin was turning gray and she had lost more than half her blood volume. **Trevor Hackman** (MD '03, General Surgery Resident '08) was two months into his residency at Pitt, when, he says, "Something clicked in me. I started barking out orders, and we eventually saved her life." Hackman later cried for three hours at home, realizing how much he wanted to be a surgeon. Now, he is finishing a head and neck surgery fellowship at Washington University in St. Louis. And he has helped develop methods for skull base reconstruction after endoscopic brain surgery—work that Hackman was introduced to here in Pittsburgh. As a new assistant professor of otolaryngology at the University of North Carolina, Hackman says that he won't forget that fateful morning in the OR. "It made me realize I could do things to shape a person's life."

Matthew Scotch (Biomedical Informatics PhD '06), associate research scientist at Yale University, is an advocate of "One Medicine," the notion that physicians, veterinarians, and agriculture and wildlife officials should share medical knowledge to improve the health of all species. With funding from the National Library of Medicine, Scotch is trying to integrate data from departments of agriculture and departments of health into a system that predicts the risks of particular zoonotic diseases, infectious diseases transmittable between humans and animals. He is the curator of the Canary Database, developed by a Yale colleague, which includes thousands of indexed articles related to animals as sentinels for human disease. —*Brandon Ellis*

W. GREGORY FEERO

CONFOUNDING EXPECTATIONS

When **Greg Feero** (MD/PhD '98) graduated from the University of Pittsburgh School of Medicine, he achieved a first for the school's Medical Scientist Training Program (or MSTP, also known as the MD/PhD program). He was the first graduate to, by sheer choice of residency, utterly stun and perplex the mentors who had guided him through seven-plus years of scientific and medical education.

"I said, 'Look, guys. I want to do family medicine,'" he recalls.

Feero's mentors expected him to enter a highly specialized area of medicine and to publish original, transformative, biomedical research. Feero, whose PhD is in human genetics, had done extensive laboratory investigation into the barriers to delivering new genes to skeletal muscles. He hoped to someday develop a gene therapy for muscular dystrophy.

"I was being groomed to become a neurologist," Feero says. But for his last clinical rotation in medical school, he arranged to spend a month at Maine Dartmouth Family Practice. Amid the forests, rivers, and small towns of rural Maine, he was an odd duck as an MD/PhD student. For a scholarly paper, he wrote about the coming collision of genomics and primary care. It was unlike anything any other intern had done.

Months later, he transferred out of his neurology residency and into the Maine Dartmouth Family Residency Program, which prides itself on having 60 percent of its trainees go on to practice in a rural setting.



MAGGIE BARTLETT, NHGRI

Feero blends family practice and genomics

Today, Feero remains a rare bird: He's a clinical associate professor of family medicine at West Virginia University, caring for patients in a quiet corner of the Mountain State called Harpers Ferry. At the same time, he is the chief of the Genomic Healthcare Branch of the National Human Genome Research Institute in Bethesda, Md., and senior adviser to the director of NHGRI for genomic medicine.

His area is the ongoing collision of the Human Genome Project and family medicine. Family physicians, he says, cannot ignore the implications of genome-wide association studies, which attempt to tease out the genes that confer risk for, say, heart disease or diabetes.

For example, says Feero, "if you are unlucky enough to inherit the worst risk markers for age-related macular degeneration at several particular points on your genome, your risk goes up 250-fold for getting AMD. That's a small percentage of the population—1 in 25,000 individuals—but if you inherit that 250-fold risk increase, you should definitely not be smoking. You might want to be on vitamins to prevent AMD."

Because genetic risk isn't always so clear, however, Feero thinks the lasting impact of genome-wide association studies won't be in disease risk prediction—it will be in identifying new target pathways for drug development and preventative approaches. Nobody would have guessed that a gene for a protein in the blood that helps regulate inflammation was involved in AMD, he points out. But the discovery of that connection suggests a paradigm-shifting strategy for treating AMD.

Feero eyes family medical histories as powerful genomic instruments. In 2004, the U.S. surgeon general and NHGRI created a Web-based tool for recording family history. However, it required the patient to store the data, print it out, and carry it to the physician. Feero thought the tool should be compatible with electronic health records. Today, you can use it to record your family medical history (at www.familyhistory.hss.gov). And if your health care provider has secure e-mail, as UPMC does, you can send it directly to your electronic health record.

The next step, which Feero is working on, is to create simple tools for physicians to interpret this data for specific health risks. —*Chuck Staresinic*

Kevin Judy (MD '84) started the brain tumor center at the University of Pennsylvania Neurological Institute in 1992 after moving there from Johns Hopkins University. Judy's current research focuses on finding more effective methods of delivering radiation treatment. In one method, Judy implants a balloon in the abscess where a tumor once was. Catheters connect the balloon to the base of the skull, where Judy injects radioactive fluid into the balloon. After the appropriate amount of radiation has been administered, Judy aspirates the radioactive fluid from the balloon and removes the balloon.



Withers



Whitney

Judy recently spoke in front of a group of medical students at Penn when he saw a nametag that read "Katie Baratz." He asked if she knew any Baratz's from Pittsburgh, and Katie was impressed that he pronounced her name correctly (with the emphasis on the first syllable). Explanation: Katie is the daughter of Judy's Pitt med classmates Mark and Arlene Baratz (both MD '84).

"I was Baratz, she was Brown, and we were sitting right across from each other," recalls **Mark Baratz**. Mark and Arlene shared lab space in the first months of medical school. They squeezed their wedding into a weekend-long break between their third and fourth years of school, and had their first daughter, Katie, during their residencies. Mark completed his Pitt orthopaedic surgery residency in 1989, and Arlene completed her radiology residency in 1990.

Arlene Baratz, a private practice breast radiologist in Pittsburgh, has become involved with a support group for androgen insensitivity syndrome (AIS), a disorder of sexual development in which girls have XY chromosomes but otherwise develop as women because their bodies do not respond to androgen. Her oldest daughter, Katie, was diagnosed with AIS at age 6. She and her mother have talked about it on *The Oprah Winfrey Show*, and the diagnosis fueled the younger Baratz's interest in practicing medicine.

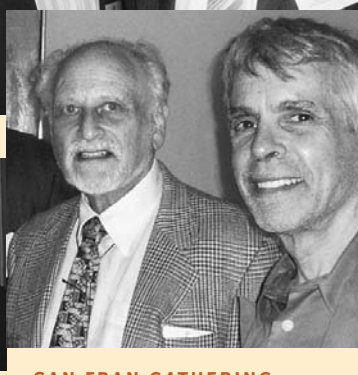
Mark Baratz is a professor of orthopaedic surgery at Drexel University with a focus on patient-directed research. For patients with arthritic thumbs, he designed a device composed of five different-sized knobs to simulate everyday tasks like turning a key or using a can opener. By measuring torque, it gives patients a practical standard to monitor their progress.

Last year, Mark Baratz pulled out his blues harmonica and played a benefit concert for his old classmate **Jim Withers** (MD '84). Baratz's blues band collected eight trash bags of winter clothing and raised $1,500 for Withers' street medicine program, Operation Safety Net. Withers first realized the importance of building long-term relationships with patients when he accompanied his dad on house calls in rural Pennsylvania. After working with leprosy patients in India in his fourth year of medical school, Withers knew he wanted to help marginalized people. Now, Operation Safety Net, which puts more than 100 student volunteers on the street to treat Pittsburgh's homeless, is being used as a model by other cities. Withers is coordinating the fifth International Street Medicine Symposium in Atlanta, for the Street Medicine Institute, a nonprofit he founded to help cities around the world start their own such programs.

Jim Withers remembers **Tim Whitney** (MD '84, Plastic Surgery Resident '93) as the most creative member of the class. But Whitney recalls being humbled by the amazing qualities of his classmates. Whitney came to Pittsburgh after taking a year off to kayak the rivers of Northern California. Now in private practice in Northwestern Washington state, Whitney enjoys sketching out his artistic vision for his patients before surgery. He has come to deplore television reality shows that skew perceptions of his field. He performs different procedures every day, he says, often helping patients reconstruct their bodies after cancer, surgery, or trauma. —*BE*







SAN FRAN GATHERING

CLOCKWISE FROM TOP: **Alan Burckin (MD '61), a retired pediatrician, and Michael LaFrankie, executive director of health sciences development, chat at a San Francisco reception in April before a talk by Pitt's Margaret McDonald, associate vice chancellor for academic affairs, health sciences. • Reception host David Mendelson (MD '64) is shown right with radiation oncologist Barry Chauser (MD '64). • Samuel Aronson II (MD '55) regaled guests with tales of Scope and Scalpel's beginnings. Aronson recalled one of the many characters in that first production—the lanky Ben Spock, played by Jim Finlay (MD '55), whose own significant height seemed to make him a natural for the part. The famed pediatrician stood next to the stage and laughed out loud throughout the production.**

IN MEMORIAM

'40s

JAMES DATTILO
MD '43A
MAY 22, 2009

ROBERT TYSON
MD '45
MAY 28, 2009

'50s

PAUL RITTER
MD '50
MAY 19, 2009

RUDOLPH BUCK
MD '52
JUNE 11, 2009

THOMAS GREGG
MD '53
MAY 18, 2009

WILLIAM VARLEY
MD '53
JAN. 27, 2009

VAUGHAN PETERS
MD '55
SEPT. 30, 2008

JAMES HANRAHAN
MD '56
MAY 2, 2009

ROBERT KING
MD '56
JUNE 6, 2009

'60s

LYNN DAUGHERT ARAGON
MD '60
APRIL 1, 2009

FREDERICK WUC
MD '60
APRIL 22, 2009

A NEW TARGET FOR JAN SCHNITZER

BY SHARON TREGASKIS



FRANK HARRIS

Bypassing residency for the lab, Schnitzer went straight from medical school to a postdoc in cell biology.

The way Jan Schnitzer (MD '85) sees it, for the last 40 years, scientists intent on developing a magic bullet to fight cancer have been targeting the wrong places. The problem, he says, boils down to the extension of a basic concept in tumor biology known as angiogenesis, the process of blood vessel production initiated by a tumor to make sure it has the building blocks for unrestricted growth. "The bull's-eye for most people . . . has been tumor cells," he says. Schnitzer has focused, instead, on starving out myriad kinds of cancer by understanding—and interrupting—the role of blood vessel proteins in angiogenesis. "We're trying to create magic bullets, too," he says, "but we changed the bull's-eye."

Until recently, Schnitzer was the scientific director of San Diego's Sidney Kimmel Cancer Center. With the 25 scientists in his lab, he developed techniques to image molecules in living organisms, mapped hundreds of blood vessel proteins from healthy and diseased organs, and tested targeted cancer therapies that leave healthy tissue unscathed.

"He's a prolific investigator, on the fast track to discovery in areas which people are finding very hard—how to deliver drugs and reduce toxicity," says Suresh Mohla, associate director of the Division of Cancer Biology at the National Cancer Institute (NCI). "If he can devise methods which can determine, through imaging, where the drug is being targeted, and whether the drug is effective in that area, that will go a long way to change the way we think of chemotherapy and will certainly be helpful in eliminating its side effects."

For the better part of a decade, Schnitzer's was a lone voice in the wilderness. After a string of rejections for NCI funding in the late '90s, he penned a pointed response to his reviewers—and got a grant, an event he likens to the bursting of a dam.

"It was like going from desert to fertile ground," says the scientist, who found himself at the epicenter of a hot new line of research.

"You get a lot of criticism in this business, a lot of naysayers," says collaborator David Cheresh, a professor of pathology at the University of California, San Diego. "Jan has enough determination and confidence in his own abilities to know he can overcome the obstacles that will be thrown his way."

That combination continues to yield results. Today, the Pittsburgh native holds a half-dozen patents for techniques to sample the lining of the blood vessel and the nanoscale protein repositories that dot its surface, known as caveolae. He also serves as coprincipal investigator on a $13 million, five-year program project grant from NCI to test tumor-vascular targeting agents. Schnitzer's post-MD career took a trajectory like that of a PhD in biophysics. Instead of a residency, he did a postdoc in cell biology at Yale University followed by a string of academic appointments—and a six-year hiatus to found a biotech startup called Vascular Genomics in the late '90s. He now directs a new institute, the Proteogenomics Research Institute for Systems Medicine, which is in San Diego.

"Jan's ability to cut across both clinical and translational science is a big benefit," says Cheresh, Schnitzer's co-PI on the NCI project grant. "Not only does Jan ask critical questions we'd all love to have answers to, he also designs the systems and approaches to answer those questions." ■

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EVOLVING SURVEILLANCE

University of Pittsburgh assistant professor of medicine Elodie Ghedin works with a team at the J. Craig Venter Institute and the National Center for Biotechnology Information sequencing the complete genome of individual flu viruses. The team has completed more than 3,500 different samples of flu virus in the past five years, providing the raw data the scientific community uses to try to understand how this quick-change virus evolves. In the months since an unusual strain of H1N1 influenza virus (swine flu) emerged and became a pandemic, the team has sequenced about 50 individual samples each month.

In the chart Ghedin produced (above), amino acids that make up the viral genes are color coded. Note how different this outbreak (center) is from the typical seasonal flu from 2008 (left). And though it shares similarities with other swine flu samples (right), it is quite different from those as well. The newness of the virus explains why our immune systems seem unprepared for it. The fear, Ghedin says, is that it will combine with these other circulating flu viruses and suddenly become both unfamiliar and virulent.

"Some epidemiologists say that the 1918 Spanish flu was relatively mild initially," she points out. "Then a second wave became far more devastating." Ghedin and her colleagues plan to catch viral evolution in action—to better understand this outbreak and to better prepare for future ones. ***—Chuck Staresinic***

CHART BY ELODIE GHEDIN

CALENDAR

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Neil Resnick, MD, Speaker
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KIESEWETTER LECTURE
SEPTEMBER 23
7 a.m.
Lecture Room 5, Scaife Hall
Dai Chung, MD, Speaker
For information:
www.surgery.upmc.edu

LEVY LECTURESHIP
OCTOBER 9
Joanne Jordan, MD, MPH, Speaker

BIOMEDICAL GRADUATE STUDENT ASSOCIATION RESEARCH SYMPOSIUM
OCTOBER 21
9 a.m. – 6 p.m.
Biomedical Science Tower S-100 & Lobby
www.bgsa.pitt.edu/events.asp

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OCTOBER 22–25
Pathway to Professions
Thursday, October 22
Fireworks and Laser Show
Friday, October 23
Pitt v. South Florida
Saturday, October 24
For information:
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OCTOBER 23
6 p.m.
University Club
For information:
Office of Health Sciences Diversity
412-648-2066

MUSGRAVE LECTURESHIP
OCTOBER 30
5:30 p.m.
Magee-Womens Hospital Auditorium
Fu-Chan Wei, MD, Speaker
OCTOBER 31
10 a.m.
Scaife Hall, Lecture Room 5
Grand Rounds

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