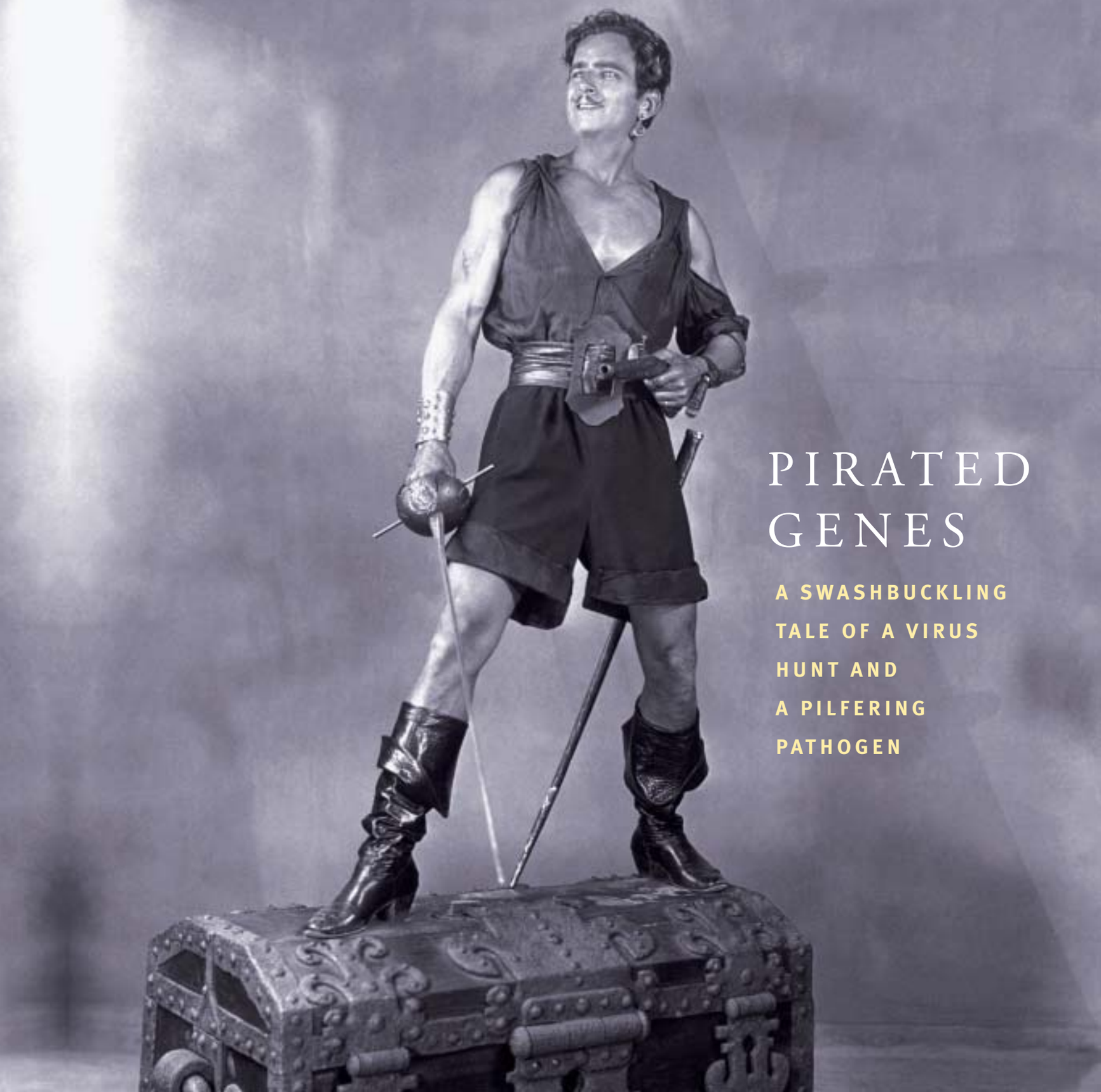
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | NOVEMBER 2003

PITTMED



PIRATED GENES

A SWASHBUCKLING TALE OF A VIRUS HUNT AND A PILFERING PATHOGEN



TIMBO AND HANK

It is a bittersweet irony that Henry Bahnson and Thomas Oliver died within four days of each other. They shared a passion for tennis, and it was not uncommon for them to play each other on a regular basis. It would probably be a disservice to their memory to reveal who was the better player, but I suspect they are again competing in order to even the score!

As one of Dr. Oliver's pediatric chief residents (he was "Timbo" to me), I can say that his greatest gift to many of us was his belief that a chief resident had the daily responsibility (yes, 365 days!) to provide clinical oversight and clinical care for a major pediatric program. The rewards for such trust were many. His chiefs grew to be skilled pediatricians—you had no choice under his tutelage. But he also established camaraderie amongst the entire lineage of chief residents. Every year, he held a party and invited every chief resident. We reminisced, drank, laughed, and, not infrequently, shed a few tears. (Timbo was known to display a gentle melancholy when a chief moved on to the "real world.")

Medicine has changed. A resident can no longer be left in charge, and "administrivia" fill the days that we former chiefs would have used to examine patients and guide the house staff. Thanks, Timbo, for leaving me something so meaningful. I will always remember our gatherings and all that you taught me.

Ian R. Holzman (MD '71)
New York, NY

A GOLDEN YEAR

Who is the real Hippocrates?
Why do medical students wear short white coats?

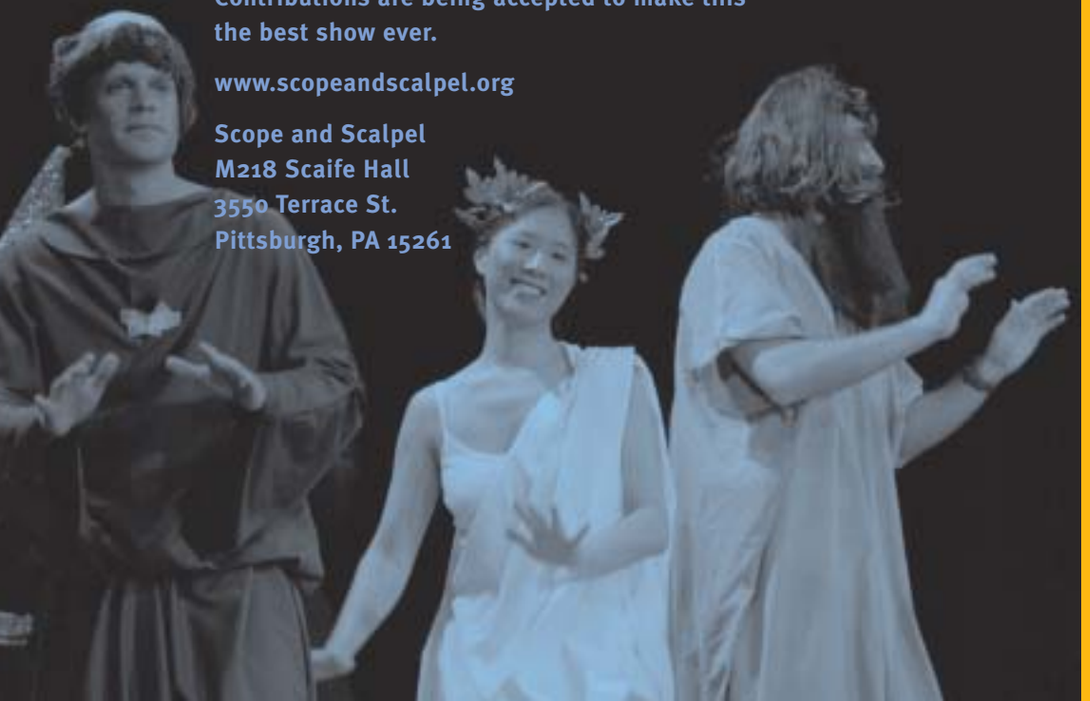
For the answers to these and other questions, don't miss the 50th production of Scope and Scalpel.

May 21–22, 2004

Contributions are being accepted to make this the best show ever.

www.scopeandscalpel.org

Scope and Scalpel
M218 Scaife Hall
3550 Terrace St.
Pittsburgh, PA 15261



C.E. MITCHELL

We welcome photos and letters (which we may edit for length, style, and clarity).

Pitt Med
400 Craig Hall
University of Pittsburgh
Pittsburgh, PA 15260
Phone: 412-624-4147
Fax: 412-624-1021
E-mail: medmag@pitt.edu
www.health.pitt.edu/pittmed

Please send address corrections to the alumni office:

***Pitt Med* Address Correction**
M-200k Scaife Hall
University of Pittsburgh
Pittsburgh, PA 15261
E-mail: medalum@medschool.pitt.edu

2003 MAGAZINE HONORS

Gold Medal, CASE Circle of Excellence
Special Interest Magazines

Gold Medal, CASE Circle of Excellence
Covers

Gold Medal, CASE District II Accolades
General Interest Magazines

Matrix Award, Women in Communications
Magazines

Renaissance Award, Public Relations Society of America
External Publications

CORRECTIONS/ CLARIFICATIONS

Our sincere apologies: In our August issue, we referred to John Kokales as Richard. Also, Geoffrey Kurland's name was misspelled.

PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE | NOVEMBER 2003, VOL. 5, ISSUE 4





DEPARTMENTS

OF NOTE 3
The School of Medicine gets a perfect score.
Cloning primates isn't working.
Modern adventures on the Lewis and Clark trail.

INVESTIGATIONS 8
Simplifying neurotransmission pays off.
Worms with migraines unearth key genes.
Progesterone delays early labor.

ATTENDING 34
Minority med students have a surrogate older sister in Paula Davis.

98.6 DEGREES 35
The Ashors plan now for future students.
New Pitt/UPMC foundation will make for a healthier academic medical center.

ALUMNI NEWS 36
Peter Safar outdanced them all.
To learn the fine art of the physical exam, students flock to Elmer Holzinger.

LAST CALL 40
Siren song.



CONTRIBUTORS

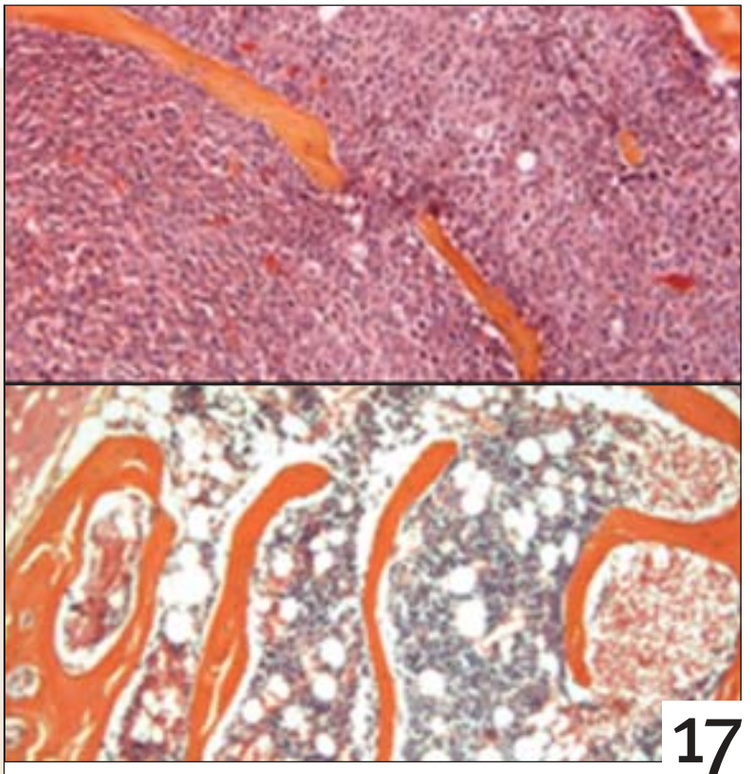
DOTTIE HORN—["Across the Divide" and "At the Heart of the Clinical Encounter"] is *Pitt Med*'s associate editor. As editor of our *Investigations* section, she has visited more laboratories on campus than anyone we know. Along the way, she has discovered that she relishes the challenge of writing about basic science. Her goal is to write in such a way that readers find themselves drawn into the investigator's story and share the excitement of the unfolding pursuit.

Veteran photojournalist C.E. MITCHELL—["Pirated Genes"] spent seven days in May documenting Western Pennsylvania for the forthcoming book *America 24/7*. He photographed inner-city barbers, an Amish family herding sheep, a young woman getting a tattoo, and many others. "This is why I'm a photographer," says Mitchell, "to step into other people's lives."

CHUCK STARESINIC—["Pirated Genes"] has joined the magazine staff as senior editor after writing and reporting for the *Allegheny Front*, *The Washington Post*, and the *Pittsburgh Post-Gazette*. While tackling the vagaries of publishing a medical school magazine, he's also been immersed in spackling and sanding his newly purchased 79-year-old home in Lawrenceville. He was spotted at a recent seminar with primer on an elbow, noting, "Sometimes it's easier not to wash it off."

COVER

It's the stuff of micro-screenplays: A virus pirates genes from the human genome. Yet by doing so, it gives scientists crucial clues to understanding cancer. (© Bettman/CORBIS. Douglas Fairbanks Sr. as the star of *The Black Pirate*, 1926.)



17

FEATURES

Pirated Genes 12
A Rosetta stone for tumor biologists, compliments of a pilfering virus.
COVER STORY BY CHUCK STARESINIC

Down to the Bone 17
Does measles cause one of the most debilitating and common bone diseases?
BY ROBIN MEJIA

Soldiering On 22
Taking roll call with Veterans Affairs; time for an often-overlooked health center to stand up and be counted.
FOLLOW-UP BY EDWIN KIESTER JR.

At the Heart of the Clinical Encounter 24
Up for examination: how doctors communicate with their patients.
BY DOTTIE HORN

First Family of Medicine 29
When Jack Myers and Jessica Lewis came to town, Pitt was forever changed.
BY EDWIN KIESTER JR.

PITTMED

PUBLISHER
Arthur S. Levine, MD

EDITOR IN CHIEF
Erica Lloyd

ART DIRECTOR
Elena Gialamas Cerri

SENIOR EDITOR
Chuck Staresinic

ASSOCIATE EDITOR
Dottie Horn

CONTRIBUTING ASSISTANT EDITOR
Meghan Holohan

PRODUCTION COORDINATOR
Chuck Dinsmore

STAFF CONTRIBUTOR
Jennifer Matson

OBITUARIES CONTRIBUTOR
Macy Levine, MD '43

CIRCULATION MANAGER
Crystal Kubic

CHIEF EDITORIAL ADVISOR
Kenneth S. McCarty Jr., MD, PhD

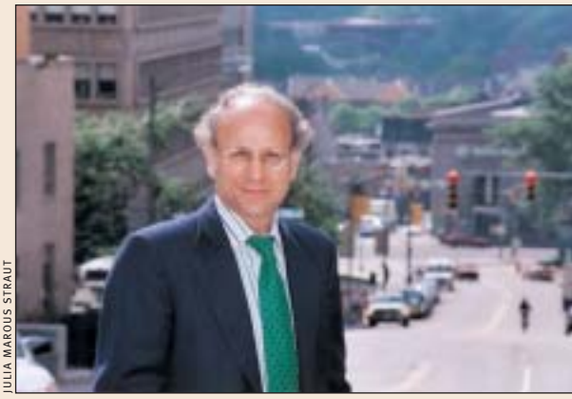
EDITORIAL ADVISORS
Steve N. Caritis, MD, Res '73
Lestina Clay, Class of '04
Paula Davis
Susan Dunmire, MD '85
Jonathon Erlen, PhD
Robert Ferrell, PhD
Jennifer Rubin Grandis, MD '87
Joan Harvey, MD
Alana Iglewicz, Class of '05
Steven Kanter, MD
Margaret C. McDonald, PhD
Ross Musgrave, MD '43
David Perlmutter, MD
Gabriel Silverman, Class of '05
Peter Strick, PhD
Simon Watkins, PhD
Marshall Webster, MD, Res '70
Mark Zeidel, MD

OFFICE OF PUBLIC AFFAIRS
Robert Hill
John D. Harvith, JD

University of Pittsburgh

Pitt Med is published by the Office of the Dean and Senior Vice Chancellor for the Health Sciences in cooperation with the alumni and public affairs offices. It is produced quarterly for alumni, students, staff, faculty, and friends of the School of Medicine. PR 4354

The University of Pittsburgh is an affirmative action, equal opportunity institution. Copyright 2003, University of Pittsburgh



JULIA MAROUS STRAUT

Shakespeare wrote, "One touch of nature makes the whole world kin." Indeed, whether we walk in the autumn woods or visualize the elegant architecture of cell membranes, as we become intimate with it, our awe in the face of nature is only likely to grow. At the same time, the quarrels and biases among humans seem dwarfed and petty in comparison. One would think that the world of medicine, where we are in the privileged position of not only studying nature but are invited into others' most private lives daily, would be flush in understanding and rich in fellowship. Yet we've much work to do. I'm thinking in particular about the disparities in health care and treatment outcomes experienced by racial and ethnic minorities in this country.

Some of this can be explained by genetic predisposition; certain people, and certain peoples, may respond less well to a drug, for instance. And disadvantaged minorities are well represented among the 44 million people in this country who have no health insurance and very limited access to care. But the problem is more complex and profound than can be explained by even these imposing factors. According to a recent Institute of Medicine report, racial and ethnic minorities tend to receive a lower quality of care than nonminorities, even when access-related factors, such as insurance status, age, education, and income, are controlled. Relative to whites, African Americans—and in some cases, Latinos—are less likely to receive appropriate cardiac medication, undergo coronary artery revascularization, or receive a kidney transplant. This epidemic of social disparity has also been documented in HIV treatment, diabetes, maternal and child health, mental health, cancer treatment, and rehabilitation. As it turns out, minority patients are more likely to refuse recommended care, adhere poorly to treatment regimens, and delay going to a physician. Yet the Institute of Medicine has found that such patient behaviors are unlikely to be a major cause of disparities.

It's not difficult to imagine that prejudicial behaviors are abhorrent to the values of most who choose vocations centered on caring for others. Yet studies suggest that elements of the modern health system can breed inequity. An economically driven lack of time, subtleties of communication, and an imprecise sense of a patient's culture, family, community, and environment encourage physicians to take "cognitive shortcuts" that may stem from misperceptions among the most well-intentioned of us. We can further illuminate and bring into sharp focus the root cause of inequities with a rigorous analysis that forgoes clichés. And we can begin to address inequities by providing evidenced-based medicine to all people and fostering in our students (and physicians throughout their careers) greater understanding across cultures and a more nuanced ability to communicate.

Back to the 44 million uninsured. Consider what could happen in the case of an epidemic when millions are without rapid access to care. Our early response would be compromised and the epidemic's scale greatly increased. Such thoughts are especially sobering in the wake of SARS and the possibility of the Soviet bioweapons program being sold off to rogue states. In these times, a grave note might be added to the already piercing words of the poet Langston Hughes: *What happens to a dream deferred? Does it dry up like a raisin in the sun? ... Maybe it just sags like a heavy load. Or does it explode?*

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

"HARLEM" REPRINTED WITH PERMISSION RANDOM HOUSE / KNOPF



Devoted to noteworthy happenings at the medical school . . . To stay abreast of school news day by day, see www.health.pitt.edu

Change of Heart

As an undergrad, Hameed Aziz (Class of '05) did grunt work for his more senior lab partner. This confirmed his suspicions: He hated research. But when his partner left, he took on more responsibility; pretty soon he discovered that this research stuff was pretty exciting. Recently, Aziz received a Sarnoff Fellowship, which allows him to spend a year in a cardiology lab. The Stanley J. Sarnoff Endowment for Cardiovascular Science awarded eight fellowships to med students this year. Ultimately, Aziz chose to work with Michael Sack at the National Institutes of Health, where he studies mitochondrial biogenesis in relation to diabetes. But first, Aziz spent a marathon two weeks in July zigzagging across the country to select the institution where he would spend his fellowship year—interviewing at UCLA, Duke University, and elsewhere. His last stop was at Harvard University. He'd had no time to buy another plane ticket, so Aziz took an 8:45 p.m. red-eye bus back to Pittsburgh. Why the rush? He'd promised another student that he would help him with his research project in the morning. ***—Jennifer Matson***

STEPHANIE HOOTON/PICTOGRAM STUDIO



Aziz at the NIH

LCME GIVES PITT PERFECT SCORE

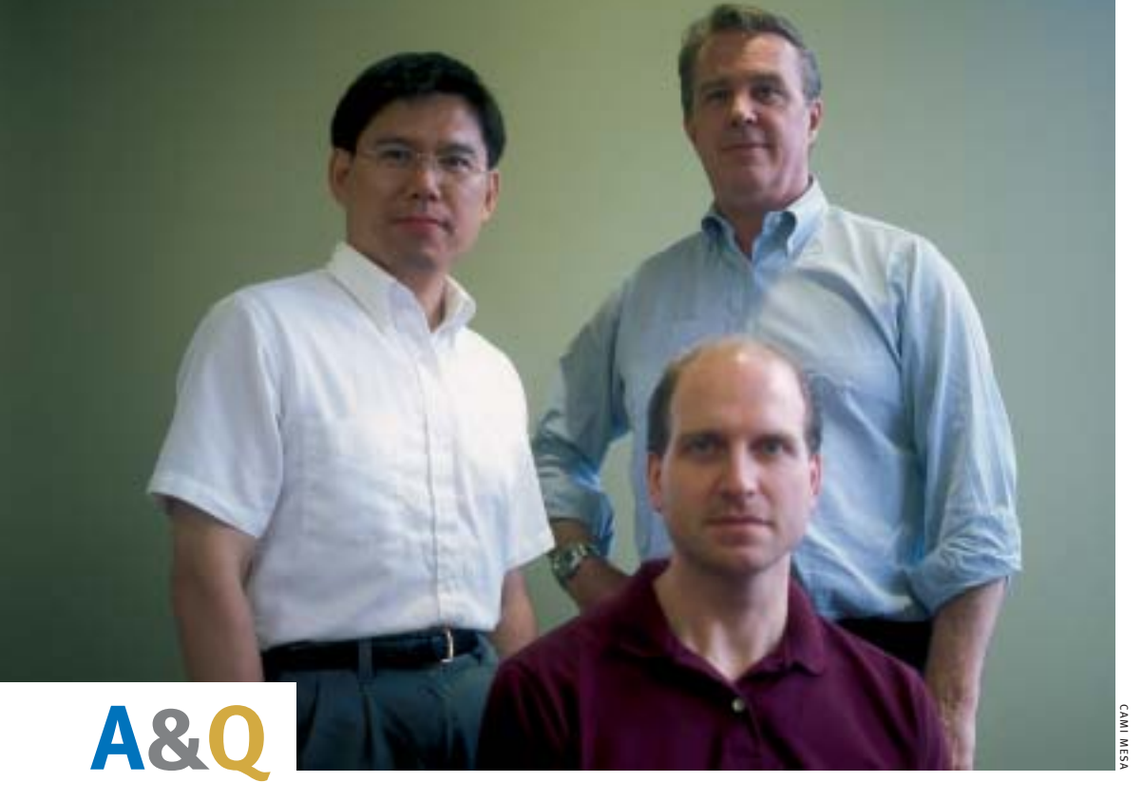
This year, Pitt's School of Medicine received a "perfect score" from the Liaison Committee on Medical Education, the group that accredits all MD-granting institutions in the United States and Canada. In other words, the school has fully complied with all accreditation standards. "Only a few medical schools have ever received that distinction," says Steven Kanter, vice dean of the medical school.

The school was reaccredited for the maximum period of eight years, after an intensive 18-month process. The final step occurred in March, when LCME officials visited the school for four days, meeting with about 100 people. Kanter was especially pleased with the LCME's long list of the school's strengths, which included its responsiveness to student concerns. One example of that responsiveness, says Kanter, is the area of concentration program, which allows students to earn certificates in areas of interest. "The AOC program was initiated by two students coming to me with some ideas and dreams," says Kanter. "We recruited some faculty and turned it into a reality. That kind of thing doesn't happen at every medical school." ***—Dottie Horn***

MIND IF WE GUSH?

When reaccrediting the School of Medicine, the LCME took note of the school's strengths, especially...

- **"outstanding" leadership, vision, and responsiveness to student concerns**
- **"outstanding" student recruits**
- **a simulation center bar none**
- **"energetically committed" faculty**
- **the success of its research enterprise**
- **a strong partnership with the medical center**



CAMI MESA

A&Q

with RODS Team Leaders

If somehow a lot of people in your town ended up in the ER because of respiratory distress, Pitt's Mike Wagner (in blue shirt), an associate professor of medicine and intelligent systems, and lab colleagues William Hogan (red shirt) and Fu-Chiang Tsui (in white) might notice a blip on their computer screens. Wagner's lab developed RODS, Real-time Outbreak and Disease Surveillance. RODS ties into ER data to alert health officials of potential disease outbreaks. A new project coming out of their lab, the National Retail Data Monitor, collects daily sales data from pharmacies, groceries, and warehouse stores like Sam's Club on the quantity of products sold that could be used to relieve symptoms of infectious diseases (including the value pack of toilet paper you just bought). As with RODS, the data are made available each day to local health departments and the Centers for Disease Control and Prevention.

On what they were thinking when they first heard about SARS

Tsui: "It struck me that SARS, like other bioagents, could easily cause tremendous damage to a country in terms of the social-economic impact as well as on people's lives, and it could do so within a very short period of time."

On how biosecure they're feeling these days

Wagner: "I'm feeling secure about contagious diseases like monkey pox and SARS, where a good [containment] response is the main issue. But I'm not feeling very biosecure about… contaminations of the air, food, or water, where a lot of people will get sick suddenly, at the same time, and then, if it's a lethal disease, they'll all proceed to terminal stages. The window of opportunity for intervening is very narrow. The first sign of a problem is that everyone is sick. And that means you've already incurred a lot of morbidity."

On vaccinations for smallpox

Hogan: "I would get the smallpox vaccine. SARS demonstrates very clearly the problems that arise when hospital workers contract the disease they are trying to treat. However, the risk of the vaccine must be balanced with the likelihood of an attack. Hospital workers in large cities like New York and D.C. should probably be vaccinated, whereas hospital workers in small rural towns probably should not. I would, however, ultimately make the vaccine available to anyone who wants it and would force no one to get it against their will."

On what else we could be doing to prepare for an outbreak

Wagner: "[Systems to help detect] rare diseases a physician might overlook. A lot of the diseases of interest to public health are febrile pneumonic illnesses: influenza, tularemia, plague, anthrax… I'd like to see, and we will see, though it's going to take a lot of time, maturation of clinical information systems [to report such illnesses in real time]."

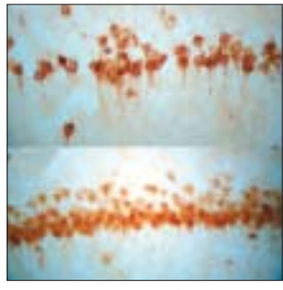
Their question for the world

"What can you do to help the RODS project to protect the public's health?"

—Interview by Erica Lloyd with Cleat Szczepaniak

Faculty Snapshots

On an average day in Pittsburgh, one person's heart suddenly stops beating. Out of every 100 of these sudden cardiac arrest cases, paramedics are able to restart the heart in about 30 people. Sometimes, the heart stops again while the ambulance speeds to the hospital; about 25 of those 30 will live to be admitted. Once they arrive at the hospital, doctors can usually keep the heart beating, but the patients are often in a coma from brain damage suffered while the heart was stopped—on average, eight will survive the coma out of every 25 admitted. Clinical studies have shown that hypothermia treatment (lowering the body temperature) helps increase survival in those who make it to the hospital alive. In treating sudden cardiac arrest patients, **Clifton Callaway**, assistant professor of emergency medicine, uses cooling blankets, and sometimes pumps cold water into the stomach, to lower body temperature to about 93 degrees. Using an animal model, Callaway has shown that hypothermia treatment after cardiac arrest results in higher levels of certain trophic factors, which nourish the brain. These factors seem to promote brain recovery.



More neurons (stained red) survived in the rat that Callaway's lab cooled during resuscitation (bottom) than in the rat they resuscitated at normal temperature (top).



Belani

Oncologists often treat elderly patients with less aggressive regimens than younger patients receive—with all types of cancer, says **Chandra Belani**, professor of medicine. In nonsmall cell lung cancer (NSCLC), for example, the standard of care is a combination therapy involving two drugs. Patients in their 70s and older, however, are often treated with only a single drug or with lower doses of the drugs, because of concerns about how they will tolerate the treatment. Belani's research has shown that, in general, NSCLC patients ages 70 and older who received combination therapies (involving the drugs paclitaxel and carboplatin) had rates of survival and side effects similar to those of younger patients who received the same treatments. His findings were presented at the American Society of Clinical Oncology meeting in May. *–DH*

MONKEY CLONING FAILS

Take an egg cell from cow A and pull out the DNA with a pipette. Replace it with DNA from a cell from cow B. The egg cell starts to divide, and if inserted into a surrogate mother, may develop into a new animal that has the exact same DNA as cow B. That's cloning. It has worked in cats, sheep, cows, and other species, but not in primates.

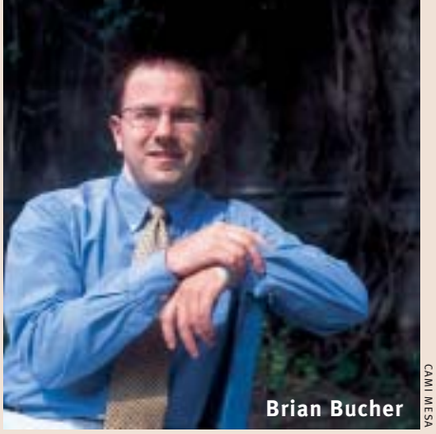
In a recent *Science* article, Gerald Schatten, Pitt professor of obstetrics, gynecology, and reproductive sciences and of cell biology and physiology, reported on his team's failure to clone rhesus monkeys. The Pittsburgh Development Center research team, which Schatten leads, discovered that the monkey egg is very different from the eggs of other animals in which cloning succeeds. After a monkey egg is first cloned, the egg divides, but the mitotic spindle that helps pull the chromosomes apart does not form properly. "From the outside, it looks as if you have a terrific cloned embryo, but at a genetic level, each of the cells has the wrong number of chromosomes," says Schatten. None of the embryos his group implanted into surrogate mothers resulted in births.

Cloned monkeys, Schatten says, could advance stem cell research and help scientists tease out how genetics and environment interact to produce disease. His lab has garnered $6.4 million from the National Institutes of Health to test an alternative method of cloning, which Schatten developed.

Although cloned primate cells could lead to new therapies for people, Schatten emphasizes that reproducing humans through cloning should never be attempted. "Human reproductive cloning is unsafe, unethical, and ought to be illegal," he says. *—DH*

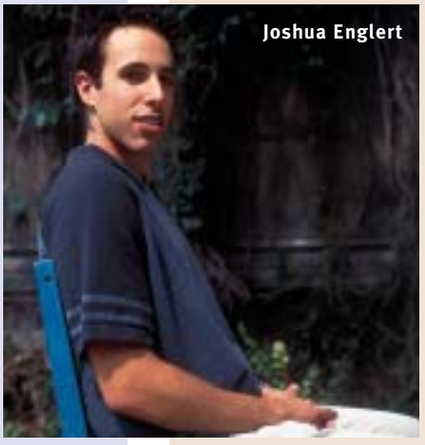


Francesca Coppelli



Brian Bucher

CAMI MESA



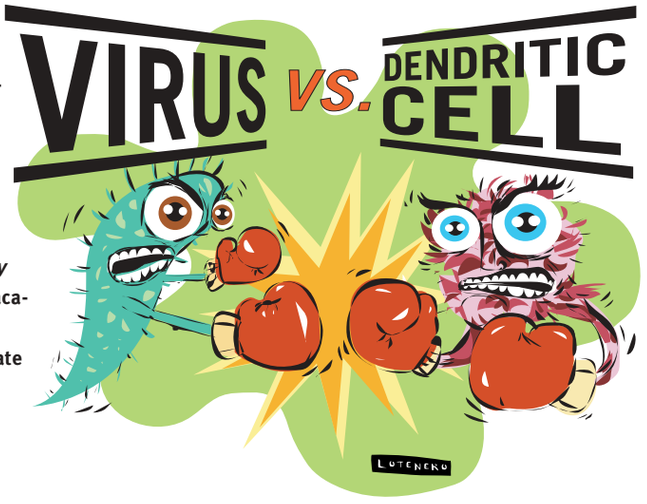
Joshua Englert

Ready for the Unexpected

Brian Bucher (Class of '06) tags this quote by Isaac Asimov to all his e-mails: "The most exciting phrase to hear in science, the one that heralds the most discoveries, is not 'Eureka!' (I found it!), but 'That's funny...'" Although Bucher is still waiting for his "that's funny"—i.e., "that's unexpected"—moment, he's hoping it will come soon. Maybe even this year. Bucher is taking off a year from school to pursue liver transplantation research with the Department of Surgery's David Geller (Res '96). He, along with Francesca Coppelli (Class of '05) and Joshua Englert (Class of '05), received Howard Hughes Medical Institute (HHMI) extramural fellowships to spend a year conducting research. The fellowship, awarded to 60 students nationwide, includes a $21,000 stipend. Coppelli is researching the epidermal growth factor receptor with Jennifer Grandis (MD '87), associate professor in the Departments of Otolaryngology and Pharmacology. Englert is studying a novel anti-inflammatory compound that has potential to treat conditions like sepsis and hemorrhagic shock. His mentor is Mitch Fink, chair of the Department of Critical Care Medicine. Two other Pitt med students were awarded HHMI cloister fellowships to study at the National Institutes of Health. (More on those coveted prizes in an upcoming issue.) *–JM*

Not Just a Game

"I'm gonna give you pneumonia!" said the eighth grader in the school cafeteria. "Well, I have a neurotrophil to defend against that!" his classmate replied, slapping a card onto a board game. Richard Steinman, associate professor of medicine and pharmacology at Pitt, listened to the teens and was thrilled by how animated they'd become as they played the educational game he developed called BioBattles. Steinman had come up with the idea while watching his own kids play Pokemon. Amazed by the incredible amount of detail they remembered from the cards, he thought, *Why not develop a card game about the constant battles being fought by the immune system in our bodies?* When he and his kids were on vacation, they made a prototype. Later, he received an Innovation in Education Award from Pitt's Provost's office to create a more elaborate product. He's now in discussions with a company about commercializing the game as he tests it formally and informally. It appears that both middle school students and med students score higher on immune system quizzes after playing BioBattles. *–JM*





CARNEGIE MUSEUM OF ART PITTSBURGH/THE CHARLES "TEENIE" HARRIS ARCHIVE

Trust Your Barber

Some people tell the barber things they would never say to a doctor. So Stephen Thomas, director of Pitt's Center for Minority Health in the Graduate School of Public Health, is turning barbers and beauticians into lay health advisers for a population that's been traditionally reticent about getting regular medical care. Stylists at nine African American shops and salons around Pittsburgh are being trained to recognize and discuss conditions their customers might have, like diabetes, obesity, asthma, and even cancer. So, how about a shave with that haircut? And have you asked your doctor about that mole yet?

FOR MORE INFORMATION:
www.cmh.pitt.edu

Appointments


Peault

Most adult human tissue contains stem cells—but at very low proportions. In adult bone marrow, for example, there is only one stem cell for every 10,000 cells. In embryonic tissue, stem cells are much more numerous and active—making them more accessible to researchers like **Bruno Peault**. A PhD, Peault recently came to Pitt as a professor of pediatrics and cell biology and physiology, leaving the Centre National de la Recherche Scientifique in Paris. Using embryonic tissue, Peault studies hematopoietic stem cells (which are the precursors to mature blood cells). He has discovered a new location in the embryo that is a source of hematopoietic stem cells. "It's a small body of stem cells that establishes the pool of blood stem cells that functions during the whole life of the adult," says Peault. He is now trying to identify populations of stem cells in the lining, or epithelium, of the human airway. The epithelium may use stem cells to repair damage caused by smoking, asthma, or cystic fibrosis.

Hepatitis C ravages the liver—and is the reason for half of the liver transplants that take place in the United States every year. When a hepatitis C patient receives a new liver, it inevitably becomes infected with the virus—and some of these people will require second and even third transplants. So, does the level of immunosuppression affect whether the new liver is ultimately destroyed by the virus? **Thomas Shaw-Stiffel**, an associate professor of medicine at Pitt, is helping to answer this question by studying drug metabolism. He's looking at the genetics of drug clearance in people before they undergo transplants, which could help him determine how much to immunosuppress, particularly in patients with hepatitis C. The MD came to Pitt last year from the University of Rochester in New York.


Shaw-Stiffel

In African Americans, colon cancer is 25 times more common than it is in native Africans. "We're investigating the differences in the bacterial populations between African Americans and native Africans and seeing whether this is related to colon cancer risk," says **Stephen O'Keefe**, an MD/PhD who came to Pitt this year, leaving Virginia Commonwealth University. Other studies have shown that certain types of bacteria in the colon will metabolize undigested food into toxins that increase the risk of colon cancer. O'Keefe, a professor of medicine, is also studying a new way to feed patients with acute pancreatitis. (If these patients eat normally, their disease often becomes worse.) O'Keefe delivers nutrients using a tube that is inserted through the nose into the digestive tract, avoiding the problems associated with intravenous feeding. *–DH*


O'Keefe

2,000 MILES AND 26 TEENS: ON THE LEWIS & CLARK TRAIL

BY JENNIFER MATSON AND DOTTIE HORN







COURTESY LANTZMAN

Eric Lantzman as a flower child and other scenes from the med student's journey on the Lewis and Clark trail with youth artists. BOTTOM LEFT: The teens learn a Native American dance.

Eric! Eric Lantzman (Class of '05) heard his name called from the edge of the Missouri River and saw a girl—one of 26 Pittsburgh teens he was traveling with through wilderness areas—lying facedown on a dock. Her throat was tightening, and she was losing feeling in her fingers and toes because of severe dehydration. Someone helped Lantzman flag down a boat. Onboard, he covered her with river-drenched towels and put a paper bag over her mouth to control her hyperventilation. He treated her until they reached an EMS crew downstream; there, the girl stabilized.

As the medical guide on a Manchester Craftsmen's Guild–sponsored trip for inner-city teenagers that traced the Lewis and Clark trail (the trip celebrated the 200th anniversary of the expedition across North America), it was Lantzman's job to handle medical emergencies like this one. The med student was trained as an EMT in high school in Mt. Lebanon. He's used to crises and expected this sort of thing. What he may not have expected from the trip was how much new territory both he and the teens would cover by taking the storied trail.

With the teenagers, he jumped off a 30-foot cliff into the Missouri River, but there were other splashes along the way. Like the boys who didn't want to share a hotel bed and started screaming about who was going to sleep on the floor. Lantzman defused the situation—he didn't want the teens to bear ongoing resentment against each other. "We're just here to sleep," he told them. Eventually, the boys calmed down, having learned something about compromise. And there was the girl with behavioral problems who opened up to him about her family situation: She lives with a relative because she doesn't get along with her parents. *An individual's story can really alter my view*, he wrote in his journal that night. *She has never learned to deal with her own sadness and despair, which is so debilitating.*

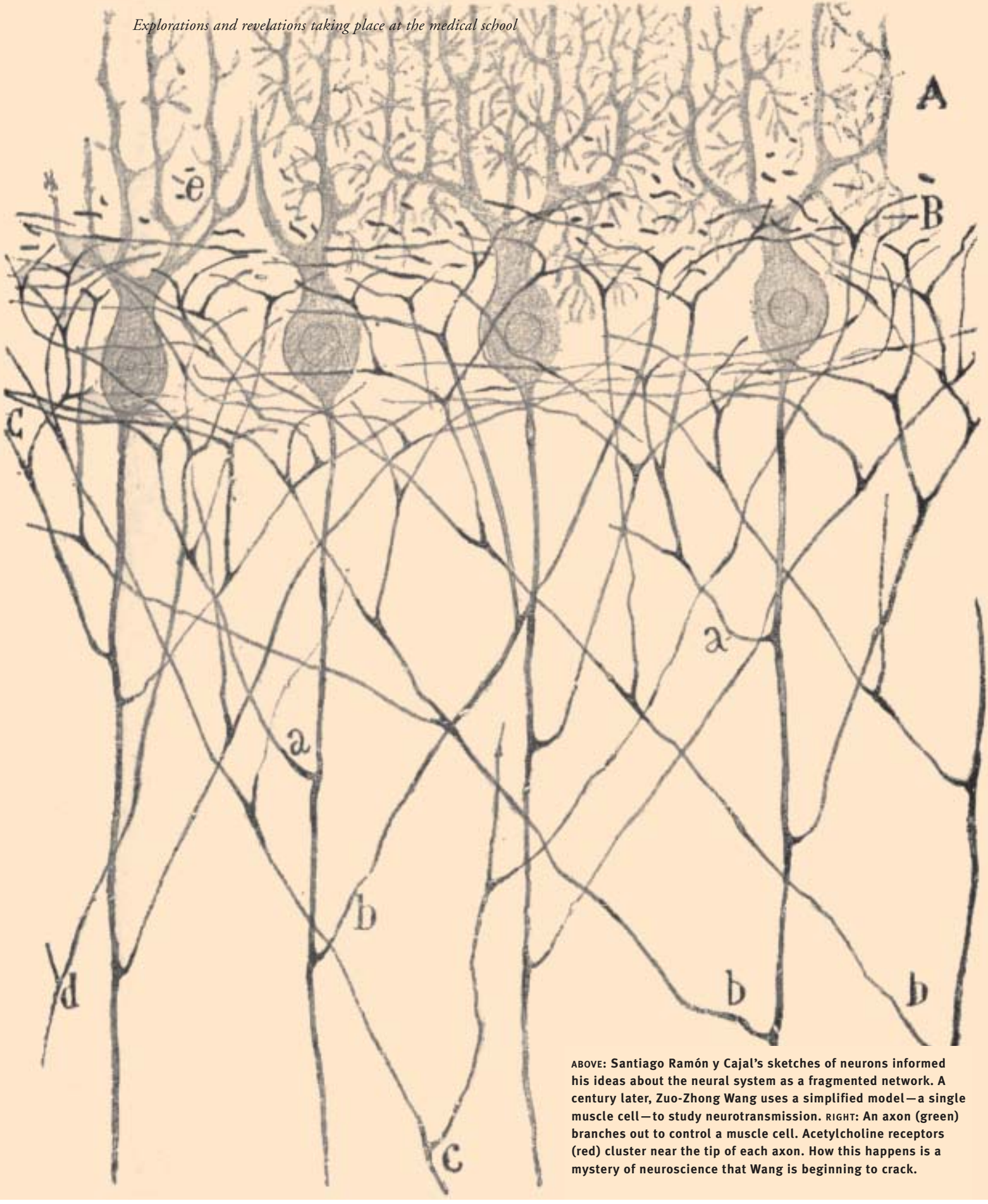
For three weeks, the group traveled by train, bus, foot, and canoe. Their bus had an area where the teens could sketch or press flowers. All of the teens—some of whom are "incredible artists," notes Lantzman—take art classes at Pittsburgh's Manchester Craftsmen's Guild. (The Guild has been celebrated for its efforts to build hope and interconnectedness in urban communities through learning and arts programs.) The group stopped to camp and hike, and Lantzman showed them how one would wrap a sprained ankle or sling a broken arm. He taught them about the medical methods used in Lewis and Clark's day, such as placing unsterile lint in a wound to keep out infection. One night, it was Lantzman's turn to be the pupil as a few of the teens showed him some dance moves. He tried to mimic their steps, spinning, bouncing, throwing his hands in the air—to the amusement of his audience. Lantzman was happy to see that he gave the kids a good chuckle. The trip, after all, was about stretching boundaries; he wanted them to know that he, too, was willing to try something new.

And there are quieter memories from their time together. On a warm, blue-skied day, the group planned to paddle on the Missouri for several miles. Lantzman and a boy got into a canoe with a girl who'd seemed intimidated throughout the trip; she was shy and didn't say much. Lantzman sat at the back and steered. They came across another teen, who'd set out by himself. He'd rolled his boat twice and didn't want to go any farther. "I'll trade places with you," Lantzman told him. "You steer this canoe, and I'll take yours." Then the girl spoke up: "Do you mind if I take control of the boat?" Lantzman didn't mind. In the other canoe, he paddled alongside her, explaining what to do. It was bumpy going at first, but soon, she started to master the skills. "It took her no time to learn how to rudder the boat," he says. When the river trip was over, the girl, who'd been the quietest person on the trip, was all smiles, talking about what she'd done. ■

FOOTNOTE

Stolen hospital wheelchairs—they've been likened to wayward grocery carts, and they add up to costly crimes of convenience. As many as 200 have disappeared in a year at the VA Pittsburgh Healthcare System. In a recent article, the *Pittsburgh Post-Gazette* reported "the ultimate reversal in fortune" for these hot wheels: Someone from the local Giant Eagle called to let Allegheny General know one of its chairs had been left at the store.

Explorations and revelations taking place at the medical school



ABOVE: Santiago Ramón y Cajal's sketches of neurons informed his ideas about the neural system as a fragmented network. A century later, Zuo-Zhong Wang uses a simplified model—a single muscle cell—to study neurotransmission. RIGHT: An axon (green) branches out to control a muscle cell. Acetylcholine receptors (red) cluster near the tip of each axon. How this happens is a mystery of neuroscience that Wang is beginning to crack.

ABOVE: COURTESY FALK LIBRARY, CAJAL/MALOINE. RIGHT: COURTESY Z.Z. WANG

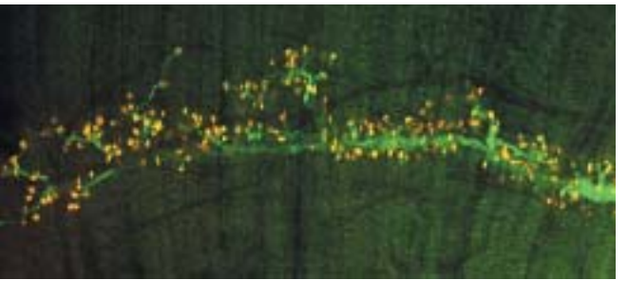
ACROSS THE DIVIDE

A TUMOR SUPPRESSOR ALSO PLAYS A ROLE IN NEUROTRANSMISSION

BY DOTTIE HORN

In 1906, two men stepped onstage to receive their shared Nobel Prize. In their acceptance speeches, they presented utterly opposing ideas. Camillo Golgi said that the nervous system was one continuous network, which ran unbroken throughout the body. Santiago Ramón y Cajal argued that the network was fragmented into a billion separate pieces—individual cells that were not continuous one with the next.

Cajal often sketched the nerve cells he'd observed under the microscope. His drawings show knobs with branches at one end and a single long straight tendril running from the other.



He guessed that the end with the branches received signals from other cells, while the lone protruding thread sent signals. Cajal was right, of course. But the story of how nerve cells communicate across the gaps that divide them is still being written today. A recent finding by Zuo-Zhong Wang, an assistant professor of neurobiology at the University of Pittsburgh, adds a surprising twist to the evolving tale.

In the decades since Golgi and Cajal offered their disparate views, scientists have established the basics. Electricity generated in the body of the cell travels down a single long protrusion (the axon). At the end of the axon are many tiny sacs of chemicals. When stimulated by electricity, the sacs spill their contents into the space between one cell and the next. The chemicals go to receptors on the branches (dendrites) of the next cell, where they may stimulate the production of a new electrical signal.

Today, researchers know that most mental illnesses are linked to problems with the transmission of signals between neurons. Many toxins—including the gas sarin, some kinds of snake venom, and the poison that causes botulism—disrupt communication between nerve cells; this can lead to paralysis, and even death. A better understanding of how neurotransmission works could lead to better treatments—so scientists strive to work out, at the molecular level, how signals travel from one nerve cell to the next.

But the brain is not easy to study. It contains 200 billion nerve cells. Each cell has hundreds or thousands of dendrites, branching like trees, and its spindly axon can extend for as long as a foot. The brain is a tangled web of crisscrossing dendrites and axons. It is difficult to distinguish which hairlike protrusion belongs to which knobby cell body or where a given signal begins and ends. To add to the complexity, a single neuron, at a single instant, can receive chemical messages from as many as 10,000 other cells. And there are more than 30 different chemicals that traverse between cells. Because of the brain's extraordinary intricacy, Wang decided to study muscle, which offers a simplified version of the connection between nerve cells.

Nerves in the spinal cord control our muscles. One axon goes from the spine to each cell in the muscle, forming a neuromuscular junction or synapse. Here there is no thicket of neuronal parts, but a single axon and a single chemical, acetylcholine, to carry the nerve's signal. There are no dendrites, but acetylocholine receptors become clustered near the axon.

Wang, a PhD neurobiologist, is interested in how these synapses form as an embryo grows. During development, before the axon reaches out from the spine, the acetylcholine receptors are spread out all over the surface of the muscle cell. Once the axon arrives, however, the receptors move until they are all clustered at the site of the axon, which rests just over the cell. If the axon is cut or the nerve is destroyed, the receptors will once again spread out all over the surface of the cell.

What brings the receptors to the axon (the process is called aggregation) and keeps them there? Wang certainly would like to find out. "We believe that the principles derived by studying the neuromuscular junction can be applied directly to the central nervous system synapses, because structurally they're very similar," he says.

To uncover proteins that are likely to be involved in the aggregation process, Wang and his lab did a three-month-long experiment. After transfecting yeast cells with mouse muscle DNA, they discovered that out of the 20,000 muscle proteins in mice, at least 14 interact with the acetylcholine receptor. When Wang looked at the list of 14 proteins, he was "very happy," as he puts it. On the list was a familiar protein, the adenomatous polyposis coli–associated protein, or APC protein. It would be easier to study than lesser-known proteins, because so much work had already been done on it.

And yet he never expected to find the protein playing a role in neurotransmission. The APC protein was discovered about 10 years ago when researchers were studying a family with a rare form of inherited colon cancer. The gene that was mutated in this family, and which caused their disease, expressed for the APC protein. Family members who had the mutant protein grew tumors. So it became known as a tumor suppressor—but researchers knew that wasn't the whole story. The APC protein is found in nearly every cell in the human body. What was its role in noncolonic cells? No one knew. "Nobody has ever thought that it's involved in neurotransmission," says Wang. His paper linking the APC protein to receptor aggregation was published in *Nature Neuroscience* in October.

"I'm excited that we are at the stage that we have the ability to solve something that was a mystery to people probably a couple of decades ago," says Wang.



The head of the transparent *Caenorhabditis elegans* worm. The bright green spots show places where serotonin is present—the worm's serotonin-releasing neurons.

COURTESY M. ESTEVEZ

WITH THE HELP OF A WORM

BY CARA J. HAYDEN AND DOTTIE HORN

MIGRAINE-RELATED GENES UNEARTHED

To the naked eye, the transparent worms look like dust motes made visible by a beam of sunlight. Under the microscope, as he watches them wriggle, squirm, and slink, Miguel Estevez can see through their skin to their organs. A Pitt assistant professor of neurology, Estevez can see that these worms are uncharacteristically sluggish because they suffer from a worm equivalent of migraine that impairs their motor coordination.

As Estevez observes the lethargic worms, a white flaming light flashes in his right eye. The light jags and squiggles, crawling along his retina like the magnified worms, and spreads across his vision. He is experiencing the visual aura that often precedes a migraine headache. Estevez himself is afflicted by the disease that he is researching.

He gets the aura symptoms of migraine, but luckily, he "grew out" of the debilitating headaches. For him, the auras are an annoyance, a common occurrence when he is stressed and sleep deprived. For others, the auras warn of days of pain. "According to my mother, she has never had a day when she was free of headache," says Estevez. (Migraines afflict a quarter of the world's population.)

Scientists know that migraine is caused by multiple genetic defects; and it's difficult to locate the particular genes that contribute to the disease. However, in the '90s, the Dutch Migraine Genetics Group studied a family with an extremely rare form of the disease, called familial hemiplegic migraine (FHM), which is caused by a defect in a single gene. People with FHM not only have headaches, but also lose coordination or become paralyzed during attacks of the disease. In 1996, the Dutch group identified the gene responsible for the family's disease—it codes for the CACNA1A calcium channel in the brain. Identifying the calcium channel, says Estevez, was a "first insight" into what goes wrong in all migraine.

For decades, scientists have known that in most adults migraine is caused by a deficiency of serotonin, a brain chemical involved in mood and memory, but they have not known what causes low serotonin levels. After the 1996 discovery, researchers explored the molecular steps leading to low serotonin levels. Understanding those steps would likely direct them to other genes involved in the disease.

To dig deeper, Estevez turned to the transparent worms known as *Caenorhabditis elegans.* (In a sense, this worm has won a Nobel. The 2002 prize went to three scientists who used the worm as a model to study the genetic regulation of organ development and programmed cell death.) Estevez chose the worms because of their genetic similarity to humans and rapid life cycle (they grow from egg to adulthood in two days). His first step was to create a worm model of FHM—he knocked out the worm equivalent of the gene defective in the FHM family. Although it is impossible to say whether the worms have headaches, they definitely have low serotonin levels and coordination problems. Estevez quantifies a worm's level of coordination by prodding it and timing how long it takes for it to complete one S-shaped crawl. Normal worms are five times faster than the knockout worms.

In the next step, Estevez took 50,000 knockout worms and treated them with a toxic chemical (ethyl methane sulphonate). The majority of the worms would be unaffected, but in some, the chemical would induce a random mutation in a single gene. He then let the 50,000 worms (they are hermaphrodites) reproduce. Each worm has 200 to 300 offspring, so Estevez wound up with some 12 million worms. About 1,200 of them had random single mutations.

Estevez then screened the mutants and identified about 20 mutations of interest. These were mutations that caused the knockout worm, which once had an abnormally pokey crawl, to slink faster and also to have improved serotonin levels. In other words, the mutation caused the worm's FHM symptoms to improve. This indicated that the mutated gene was able to compensate for the knocked-out calcium channel that otherwise would have led to a low serotonin level. It appears that the mutated gene might also be defective in some people who suffer from migraine.

Out of those 20-odd mutations of interest, one was of a TGF-beta (a growth factor) receptor gene. Estevez's additional experiments confirmed that, in worms, the receptor is involved in the process by which the CACNA1A calcium channel affects serotonin levels. "[It] is intriguing, since human families with mutations in a TGF-beta receptor gene can actually have migraine with aura.

"We've used the worm for the invertebrate studies, which are relatively easy and quick, to give us a short list of candidate genes."

Next for Estevez: Begin searching for the human equivalent of these genes in families with migraine. ■

HORMONE DELAYS LABOR

PROGESTERONE PREVENTS PREMATURE BIRTH | BY KRISTIN OHLSON



GETTY/ PORTRAIT OF A PREGNANT WOMAN, RAPHAEL, C. 1506

Every year, hundreds of thousands of pregnant women in the United States go into premature labor. Their water breaks, or they realize that the backache they've been nursing with Tylenol is actually labor, and they are rushed to the hospital, where they give birth three weeks or more short of the normal 40 weeks of gestation. Those who give birth before 28 weeks have babies who often either die or have huge health risks—they may be born blind or with cerebral palsy, respiratory distress syndrome, or other conditions.

No one knows what causes most premature births, though they account for 12 percent of live births and are the leading cause of morbidity and mortality for babies in the United States. However, clinicians at Magee-Womens Hospital and a group of other academic hospitals have finally found a treatment that helps to prevent premature labor in the most susceptible of the child-bearing population—women who've had a previous preterm birth.

For years, researchers have known that progesterone helps maintain pregnancy in animals. More than 40 years ago, studies involving periodic blood tests showed that progesterone levels steadily drop as animals approach their delivery dates. When this was discovered, researchers assumed that the same hormonal pattern would apply in humans, but daily blood tests in pregnant women didn't show the same ebb of progesterone before delivery. Despite this, a few studies in the 1960s tried treating pregnant women susceptible to early labor with progesterone. The studies showed promise, but they were small and largely discounted.

Then, in the early 1980s, Congress mandated that a portion of federal research dollars be directed to clinical studies, as some members felt that basic science labs weren't delivering enough results that applied directly to human health. The National Institute of Child Health and Human Development decided to spend this money to create a research network of clinicians from various medical centers, called the Maternal Fetal Medicine Units Network.

The network would include hospitals serving large numbers of pregnant women with complications, to ensure they would get sample sizes that were scientifically stringent, explains Steve N. Caritis. Caritis (Res '73) is a professor of obstetrics, gynecology, and reproductive sciences at the University of Pittsburgh School of Medicine and director of maternal-fetal medicine at Magee.

In the late 1990s, network researcher Paul Meis from Wake Forest University proposed a randomized placebo-controlled trial that would revisit the tantalizing promise of progesterone hinted at in those trials in the 1960s. Eventually, the new trial involved Magee, 18 other medical centers, and 463 pregnant women who'd had at least one previous preterm birth. The women were enrolled when they were between 16 and 20 weeks gestation. Two-thirds received weekly intramuscular injections of progesterone, and one-third received injections of a placebo. The results were dramatic: The women receiving shots of progesterone were a third less likely to go into premature labor. Further, the infants born to women receiving progesterone weighed more on average and were less likely to require supplemental oxygen.

"This is the first treatment that has ever reduced the rate of preterm birth," says Caritis, one of the investigators on the study, which was published June 12 in *The New England Journal of Medicine*. "Nobody knows why it works." Physicians around the country are now giving progesterone to pregnant women who have had a previous preterm delivery.

Caritis and Dwight Rouse from the University of Alabama at Birmingham are beginning a follow-up study this fall. Fourteen centers will test progesterone on another group at high risk for preterm labor: pregnant women carrying twins and triplets.

For Caritis, the progesterone breakthrough highlights the power of these networks of clinical researchers. "This study could never have been done at any one center," he explains. "Even at Magee, with 8,000 deliveries a year, it would have taken me 20 years to recruit 463 women." ■



Patrick Moore and Yuan Chang happened upon a treasure trove for tumor biologists.

ON THE HUNT FOR A PATHOGEN, THEY FOUND MUCH MORE THAN ANYONE EXPECTED

BY CHUCK STARESINIC

PIRATED GENES

Yuan Chang distinctly remembers the moment in 1981 when, during her orientation to medical school at the University of Utah, a second-year student strode to the front of the room. He was there ostensibly as a member of Physicians for Social Responsibility, but the presentation she remembers would have served equally well for a group called, say, Physicians for Unpredictable Behavior. He didn't begin with "Hello." He didn't mention his name. He didn't even say, "I'm here to tell you about Physicians for Social Responsibility." He seized the microphone and yelled, "THERMONUCLEAR WAR!"

And that was the first time Yuan Chang ever laid eyes on Patrick Moore. "What a weird duck!" she thought to herself, somewhat aghast. "How bizarre!"

PHOTOGRAPHY | C.E. MITCHELL

Perhaps in spite of this first impression, Chang soon got to know Moore in her histology class, where he was a teaching assistant. He was a set of walking contradictions and idiosyncrasies, she learned: a high school dropout who read *The New England Journal of Medicine* and frequently reminded her that she should read it, too. He plied her with journal articles, one of which made a lasting impression on both of them.

It was from the *Morbidity and Mortality Weekly Report*, a publication of the Centers for Disease Control and Prevention (CDC). ("Nobody else in medical school was reading the *MMWR*," Chang points out today with a sideways glance at Moore.) A large number of homosexual men in New York and California had inexplicably developed aggressive and rapidly fatal cases of what had always been an exceedingly rare and nonaggressive cancer—Kaposi's sarcoma (KS). One physician commented that several of these men had severe defects in their immune systems.

"This is really interesting," Moore said to Chang when he gave her the article. "You ought to keep an eye on this. This is going to be big."

The story was not big; it was colossal. It marked the emergence of the most devastating new disease of the century—AIDS. And though HIV would be identified within four years, finding a causative agent for KS—the leading malignancy in AIDS patients and the most common cancer in sub-Saharan Africa—would thwart the best efforts of laboratories around the world until 1994. That year two newcomers working on a shoestring, Chang and Moore, made the discovery that had eluded so many.

In the early days of the AIDS crisis, large numbers of patients were reported with KS as well as another previously rare condition, pneumocystis pneumonia. The latter was known to be the result of an infection, obviously made possible by the weakened immune system. But what was causing the KS?

The idea that viruses could cause human cancers was not completely new, but it was just beginning to be accepted. A virus called HTLV-1 was linked to leukemia only in 1980, human papilloma viruses to cervical cancer in 1983.

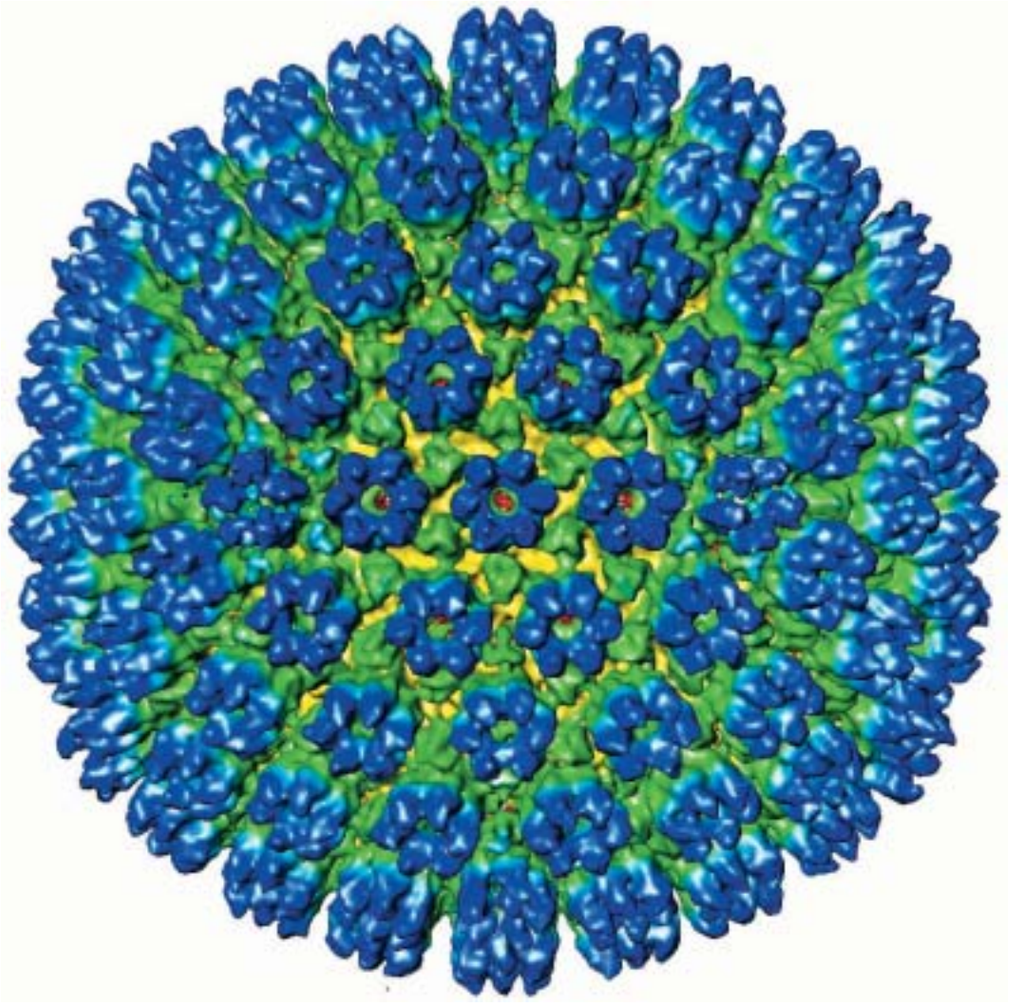
Throughout the 1980s and into the 1990s, articles regularly referred to the infectious etiology of KS. The disease appeared in patients whose immune systems were down, such as AIDS patients and transplant recipients. But not all such patients were at equal risk for developing KS. Those who developed AIDS following blood transfusions and sharing of needles rarely developed KS, while homosexual men in these groups, and especially those with a history of multiple sex partners and sexually transmitted diseases, had a greater than 50 percent likelihood of developing KS, notes Moore. It was as if a "WANTED" poster with no photograph had been hung in the town square. The profile was of an infectious agent that was sexually transmitted, more so in homosexuals than in heterosexuals.

But after a decade or more of intense investigation into KS by some of the most prominent virology labs in the world, nothing turned up. Nothing conclusive was cultured or identified. A host of alternative theories was proposed, and the search for a pathogen languished. No one was looking to Chang and Moore for the answer to what was causing KS. No one, that is, except Chang and Moore.

Moore, an epidemiologist by then, had become obsessed by the search for new pathogens. His friend Tony Marfin remembers meeting Moore in 1989, when the two were at the school of public health at the University of California, Berkeley: "Pat was talking about [KS] then. He was talking about methods that he could use to identify an infectious agent as being the cause of KS."

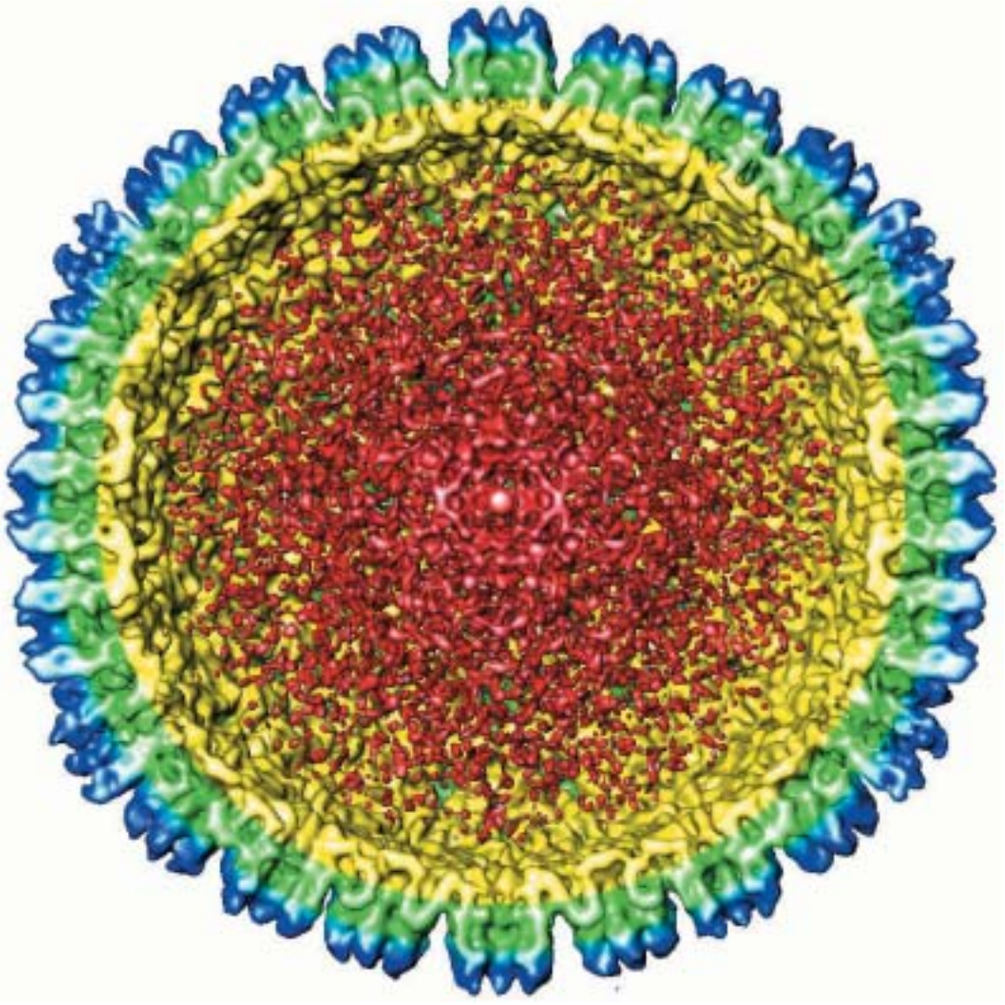
Marfin later worked with Moore at the CDC in Fort Collins, Colo., and in refugee camps in Somalia and Nepal, where Moore continued to speculate about KS. Marfin laughs now, saying, "You know, the nature of the molecular investigations for KS are not the kinds of things you need to think about or know about when you're in those refugee health situations. But he was always thinking about it then and still contributing greatly to the ongoing stuff that we were doing in those places."

Moore believed that the secret to identifying new pathogens was to develop the right tools. He remembers working in Nigeria during an unidentified disease outbreak when people suddenly began dying of hemorrhagic fever, which could be caused by a lot of things, including the Ebola virus and yellow fever. Everyone was con-



The virus KSHV pirates human genes. ABOVE: These are three-dimensional computer reconstructions of KSHV. KSHV is shown as a spherical capsid (coating) of interlocking proteins (left). The image on the right depicts a cross section. The red material represents internal components such as scaffolding proteins, amid which are the virus' genes, including those pirated from the human genome.

COURTESY Z.H. ZHOU



cerned, and samples were rushed off for tests. They were relying primarily on serologic assays, in which blood is tested for the presence of antibodies to specific viruses; they'd tested for Ebola and yellow fever. When the results came back "inconclusive," the team thought they had a new agent on their hands. Waiting for test results in the middle of an unexplained outbreak was a vivid learning experience for Moore. It showed him that epidemiologists needed a means of diagnosing a viral infection without having any preconceived notions of what the virus was. In the end, the virus was yellow fever, with atypical characteristics that made it difficult to identify, but the lesson remained.

Moore had an ideal intellectual ally and foil in Chang. The two were married in 1989. He was the epidemiologist preoccupied with the cause of KS. Chang was the clinical neuropathologist determined to come up with new techniques for identifying the causes of neurological disorders. She loved working with neurologists, neurosurgeons, and patients. With cancers in particular, she wanted to develop more powerful molecular techniques for studying them in the lab, techniques that would reveal diseases in finer detail. Visitors to their home frequently found themselves party to impromptu discussions around the dinner table exploring new methods of pathogen discovery.

Chang was recruited to Columbia University in 1993 to start a position as a clinical neuropathologist. Moore began working for New York City's health department. But more than ever he was preoccupied with the mystery of KS. Over cups of coffee at a Broadway cafe, the two talked about using Chang's lab for exploring KS. For both, it was not a question of *whether* KS had an infectious agent. The question was, how could they discover the KS agent, which had resisted all attempts at culturing?

The breakthrough arose out of Moore's habitual reading of the literature. Early in 1993, an article from *Science* emerged from Chang's fax machine at Columbia with Moore's handwriting scrawled across the title page: "Yuan, Check this out." The title was, "Cloning the Difference Between Two Complex Genomes."

Chang still has a hard time believing what happened next. It doesn't matter that it has been 10 years, and she and Moore are sitting in the lounge area of their laboratory in the new Hillman Cancer Center. Or that they have recently returned from the National Institutes of Health, where they were awarded the Charles S. Mott Prize, given by the General Motors Cancer Research Foundation, one of the most prestigious awards for cancer research. Just over a decade ago, they'd thought about KS a lot, but had never set out to find the causative agent in a laboratory experiment. Nevertheless, in six weeks, they had it. First try.

"We were really lucky"—Chang says while she almost gasps with her hand on her forehead, as if a decade hasn't been long enough to recover. Yet the process was "arduous," reports the neuropathologist who was used to getting results from an experiment in two or three days. The technique they used, called RDA, took six weeks. "This is a protocol that—my God—once you're in the middle of it, there's no way to really check whether you're on course or not," she says. "You have to go all the way through it to the very end in order to know whether you did it right."

In one shot, RDA revealed the pathogen. "It was amazing," says Chang. "We were just really lucky."

RDA, or representational difference analysis, was novel at the time. No one had yet used it to discover a new pathogen. Like a lot of breakthrough ideas, the underlying concept was simple: RDA is a way to draw out the differences between two samples of DNA; if there is a difference between KS tissue and healthy tissue from the same patient, that difference is likely to be the cause of the disease.

Chang likens the original problem to having two sets of the notoriously exhaustive, multivolume *Oxford English Dictionary* that are identical except for a few extra words hidden in one volume. Imagine how long it would take to compare the dictionaries and find those extra words. Finding the culprit in tissue samples containing enormous amounts of DNA was a similarly intractable problem. At least it seemed intractable. RDA draws out variant sequences of DNA and clones them, amplifying them so that the difference can be seen readily.

In the words of one scientist, KSHV looks like it was "made by a demented tumor biologist," because if you were going to design something to cause a tumor, these are the genes you would pick.

Moore calls KSHV the "molecular Rosetta stone" that will help us interpret the language of virology.

When Chang and Moore compared KS tissue with nondiseased tissue from the same patient, the difference between the two was a set of totally unique, distinctly herpeslike DNA sequences. They'd found another human herpes virus, the eighth yet discovered. It was soon to be called HHV8, or alternatively KSHV.

Laboratories from San Francisco to London quickly confirmed Chang and Moore's findings. More than a few KS researchers wondered who the newcomers were and from where they had come.

As exciting as the discovery of KSHV was, Chang and Moore were prepared to eventually stop studying it and move on to something else. But that has not happened, and it won't happen anytime soon. In fact, though they continue to seek out new pathogens, they call their new work space in Pittsburgh the "KSHV Laboratory" for the virus that promises to reveal a wealth of information about virology, tumor genesis, and cellular processes.

When Chang and Moore sequenced KSHV's genome in 1996, they were not surprised to find it had many genes typical of herpes viruses. The surprising thing was how many genes were recognizably human. Somehow, KSHV had pirated human genes and taken them as its own. At different times over the course of its evolution, the virus has managed to take copies of human genes from cellular RNA. The process isn't understood, but the results are dramatic.

Humans may have loads of "junk DNA" that seem to have no function, but a virus is the exact opposite. "It's got a small genome," says Chang. "It's not going to take anything extra that it doesn't need. It just spits out things it doesn't need."

COURTESY CHANG AND MOORE



Chang and Moore at the NIH, after receiving the Charles S. Mott Prize

KSHV isn't the only virus that has pirated human genes, but according to Chang and Moore, none has done so to this extent. In the words of one scientist, KSHV looks like it was "made by a demented tumor biologist," because if you were going to design something to cause a tumor, these are the genes you would pick. The virus has pirated genes related to cell cycle control, cell proliferation, prevention of apoptosis (programmed cell death), and immune modulation. In other words, it has pilfered the genetic keys to tumor growth and tumor suppression.

"Here's a virus that just laid out all this cell biology and said, 'Here, study this,'" says Moore. "You know it's so obvious: These are the things that are important for causing a tumor, and there has never been an example of a virus that's like that.

"Essentially, what you can do is walk down the genome. You can say, I recognize this gene, I know what it does in the human cell, so that means I have an idea of how to study it in the virus."

Information like this is valuable for much more than understanding KSHV. It's helping scientists learn how all viruses work and understand exactly which cellular mechanisms viruses are targeting. The presence of a pirated gene may even direct scientists to ask further questions about the gene's function in the human cell.

"In essence," Moore says, "what we and other tumor virologists are working towards is a unified field theory of tumor biology.... What we're hoping to do is to be able to say, what are the common features among all tumor viruses? KSHV is very central to that because we can interpret the other viruses in terms of KSHV."

Moore calls KSHV the "molecular Rosetta stone" that will help us interpret the language of virology.

Despite its prominence, KSHV is not the only pathogen in Chang and Moore's lab—at least, they hope it isn't. They continue to look for new pathogens with sequence-based methods like RDA.

"There are a number of different lymphomas," says Moore, "like non-Hodgkin's lymphomas and some Hodgkin's lymphomas, that have a pattern of disease that looks like they might have an infection associated with them. It's not as clear as Kaposi's sarcoma—not nearly as clear—but there's some evidence for it."

Chang brings out pictures of a rare cancer of the eye that has emerged in Uganda. The lining of the eye and lids is red and inflamed. In some cases, tumors on the surface of the eye block vision. The disease appears mainly in AIDS patients in a limited geographical area. Just like KS, it could be the result of a virus that doesn't generally reveal its presence except in severely immune-compromised persons.

There are many other diseases, rare and common, that may eventually be traced to an infectious agent. But, Chang notes, "We are likely approaching the end of our ability to identify new pathogens with simple culturing. KSHV is an example where viral fragments were found before the microorganism was cultured."

To find new pathogens that are difficult or impossible to culture, powerful molecular-based methods are required.

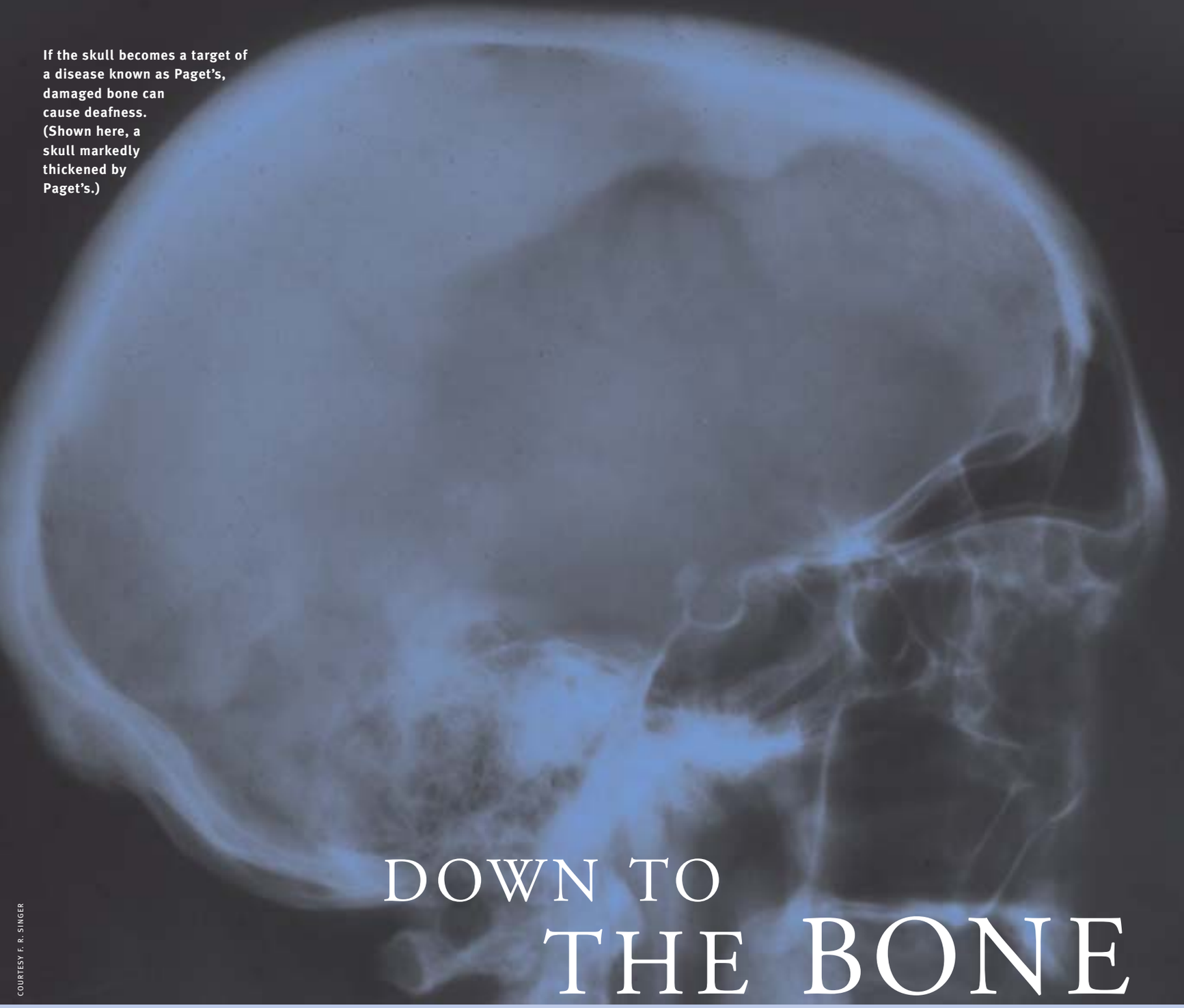
But even for a pair of now-veteran virus hunters, the odds are long, says Chang.

"New pathogen discovery is really high risk," she says. "And it can be difficult to find a place that will support high-risk research that could take years and years to notch up a discovery.

"Part of the attraction of Pittsburgh is not only the transplant population, and the pathology banking system that's here, but also just the institutional support for something like this," continues Chang. "Because we may not find anything. We hope that's not true, but if we do find something it will be because of the support of the University of Pittsburgh. We could have very well stayed at Columbia and kept on working on KSHV; but you know, we started out being virus hunters, I guess. We're very much interested in continuing to find new ways of doing that."

Those who have worked around Chang and Moore have a lot of faith in their abilities. Richard Wood is a Pitt pharmacology professor and molecular oncologist at Hillman Cancer Center. He went to Westminster College in Salt Lake City, where he first met Moore, then a fellow undergrad. Wood says that the couple has worked so well together for so long that it's hard to separate what it is that each one does differently:

"What you see when you are around them is that they are talking science all the time. It's quite remarkable. So as they pick up their kid from day care and go home, they'll start discussing an experiment. It's just constant dialogue, which I think is a really wonderful resource to have by your side all of the time." ■



If the skull becomes a target of a disease known as Paget's, damaged bone can cause deafness. (Shown here, a skull markedly thickened by Paget's.)

COURTESY F. R. SINGER

DOWN TO THE BONE

DOES THE MEASLES VIRUS CAUSE A DEBILITATING BONE DISEASE?

BY ROBIN MEJIA

Kenneth Halstead seemed too young to be suffering from bone aches. At 36, he was a successful design engineer at the Raleigh, N.C., Westinghouse plant in 1960. You may have the results of his efforts right outside your door. The plant produced most of the utility meters made in the country. His work wasn't physical labor, but it did involve a lot of walking around the 550,000-square-foot building to oversee the manufacturing of parts he'd designed. Even those walks were becoming difficult.

"When I'd get up, I'd have to walk a few steps to straighten all the way up," he says. He kept working, but it became harder to spend any length of time standing. His legs ached when he tried to straighten them. The pain kept him up at night. He started sleeping in his recliner.

Halstead's next-door neighbor, Thomas B. Dameron Jr., happened to be an orthopaedic surgeon. Dameron had Halstead come in to be x-rayed. When the slides came back, the two men looked at an image of hips covered with dark spots. Dameron said he didn't know what the spots were, so he scheduled a bone biopsy. Halstead started to worry that he might have cancer.

Two weeks later, he found out he was cancer free. He did, however, have an untreatable bone condition called Paget's disease, which he could expect to slowly worsen for the rest of his life.

Strangely, given how little-known it is, Paget's is the second most common bone disease in this country. Only osteoporosis affects more people. Most Paget's patients don't suffer the same level of pain Kenneth Halstead does. In fact, only 10 percent of the estimated 2 million Americans with Paget's complain to their doctors of symptoms. Many don't even know they have it. But for those 200,000 or so patients who experience symptoms, it can be an incredibly debilitating condition.

At a basic level, Paget's is a disease of the osteoclast. In most people, these cells keep bones healthy. As bone wears down or cracks, osteoclasts cover the damaged area and resorb it. This prepares the area for healing by osteoblasts. "People get [minor] cracks in their bones all the time," says David Roodman, University of Pittsburgh professor of medicine as well as the director of the Multiple Myeloma Center at the University of Pittsburgh Cancer Institute and a staff physician with the VA Pittsburgh Healthcare System. Without osteoclasts, the body couldn't make clean repairs. New bone would just get slapped down on top of old, creating layers and deformities.

In the case of Paget's, groups of osteoclasts go into overdrive. They become large and start devouring bone. They also limit the body's ability to lay down good replacement tissue, so most new bone is fragile and deformed. Depending on where someone gets Paget's, she might become bowlegged or lose inches from her height. Some bones are more likely to be damaged—for example, many people suffer Paget's in the hip and leg—but the disease can hit anywhere in the skeleton, affecting only one bone or many. Some patients get arthritis and fractures. Others lose their hearing.

Even though Paget's is a common disease, historically, it has been underdiagnosed. And when Halstead first noticed his problems, even a diagnosis offered little hope. In 1960, there were no treatments for Paget's; doctors could only monitor it. Halstead's case had struck unusually early in life, and it was aggressive. For the next decade, his doctors watched it worsen. Halstead ended up with Paget's in both hips, his legs, his spine, and his skull. At one point, doctors considered surgery on his spine to relieve nerve pressure, but in the end it looked like the risks outweighed the potential benefit. By 1972, when Halstead was first able to enroll in a clinical trial (for salmon calcitonin), if he tried to stand for 15 minutes, his legs went numb.

Today, doctors have many drugs at their disposal to treat the disease. However, what causes Paget's and what makes the osteoclasts go bad has until recently been a mystery. It's a mystery Pittsburgh's Roodman appears poised to unravel.



CAMI MESA

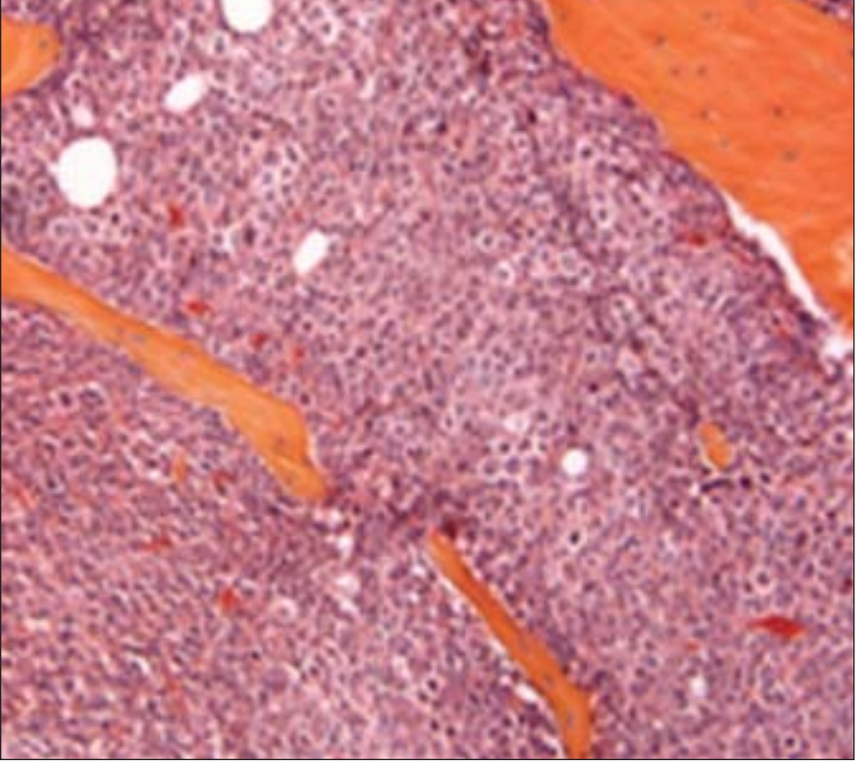
David Roodman

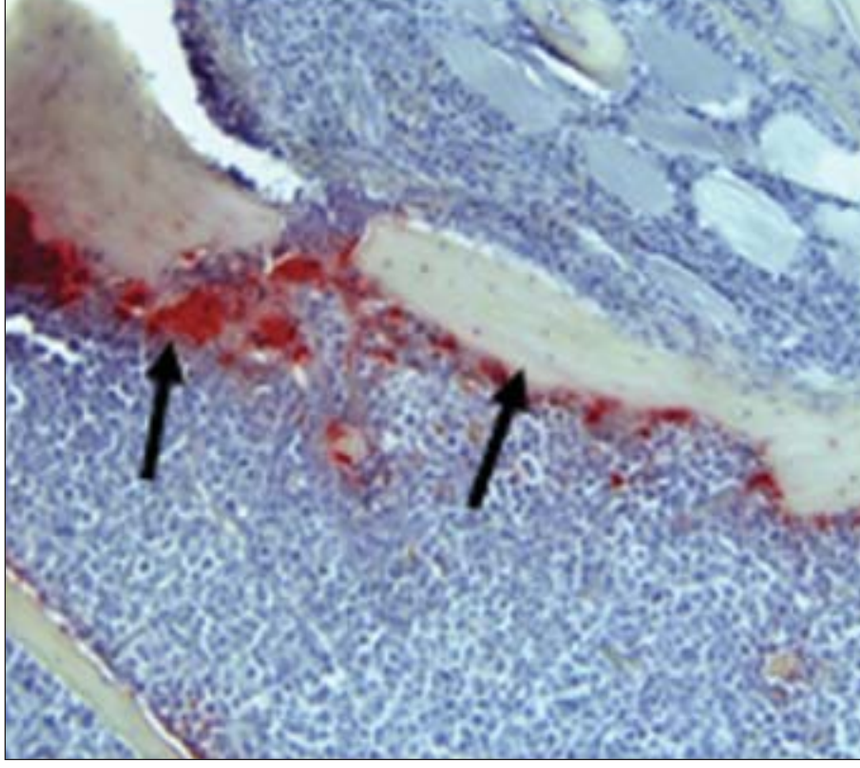
Roodman never set out to become a bone doctor. That just happened. He says that ever since he took his first genetics class, he has been intrigued by cell differentiation. In medical school at the University of Kentucky, he discovered hematology, and he's a hematologist today. (Kentucky is also where he got his PhD in biochemistry and discovered his "greatest collaborator," Mona Burton, now Mona Burton Roodman, who at the time was working in a biochemistry lab.) He says hematology appealed to his interest in how the body's precursor cells differentiate into their final state. Precursor cells in bone marrow differentiate into various types of grown blood cells. Studying blood also offered a unique advantage over the study of most internal organs, notes Roodman: "It was easy to get samples to work on."

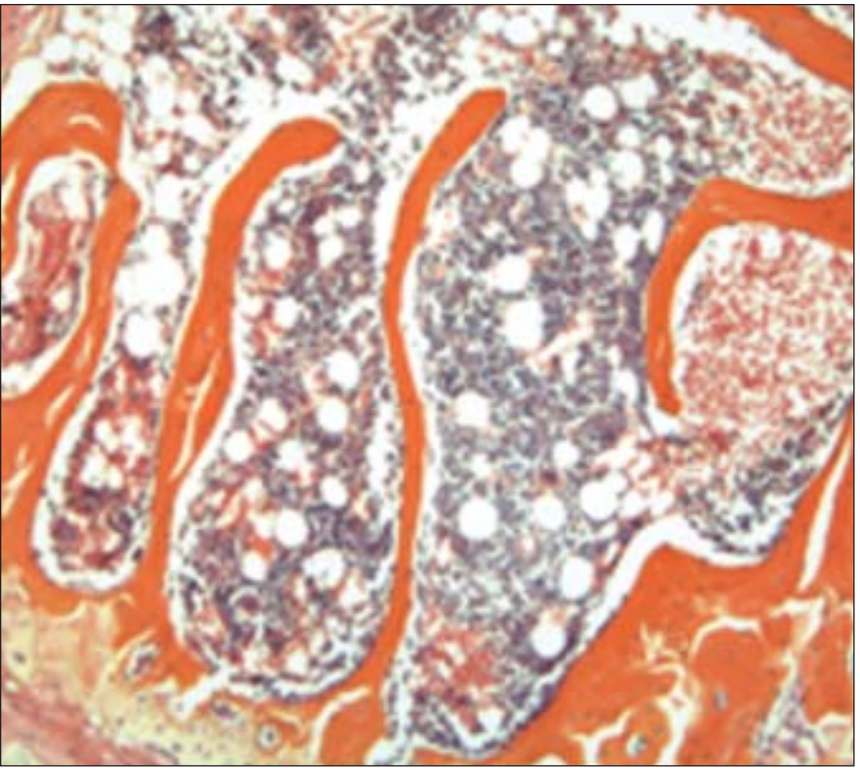
In 1980, he took a position in the University of Texas Health Science Center at San Antonio. There, he found himself in an office across the hall from the center's chief endocrinologist, Greg Mundy. Mundy was an internationally known bone specialist.

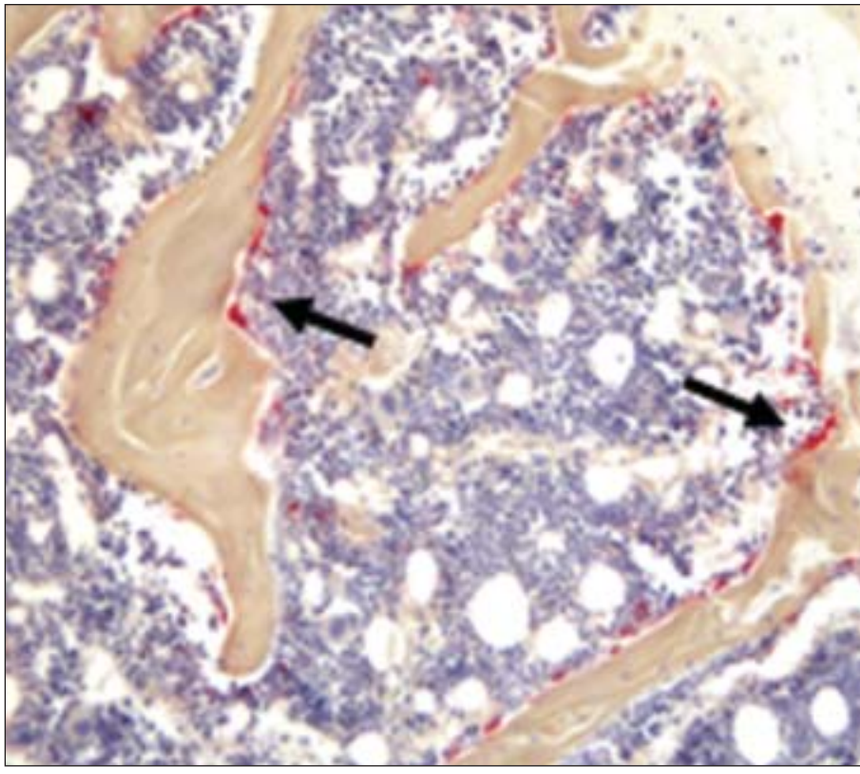
"I didn't know one end of a bone from another," says Roodman, whose influential bone studies are now supported by the National Institutes of Health, the Multiple

JOURNAL OF CLINICAL INVESTIGATION, DECEMBER 2001, VOLUME 108, NUMBER 12, 1833-1841. COPYRIGHT 2001 BY THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION.







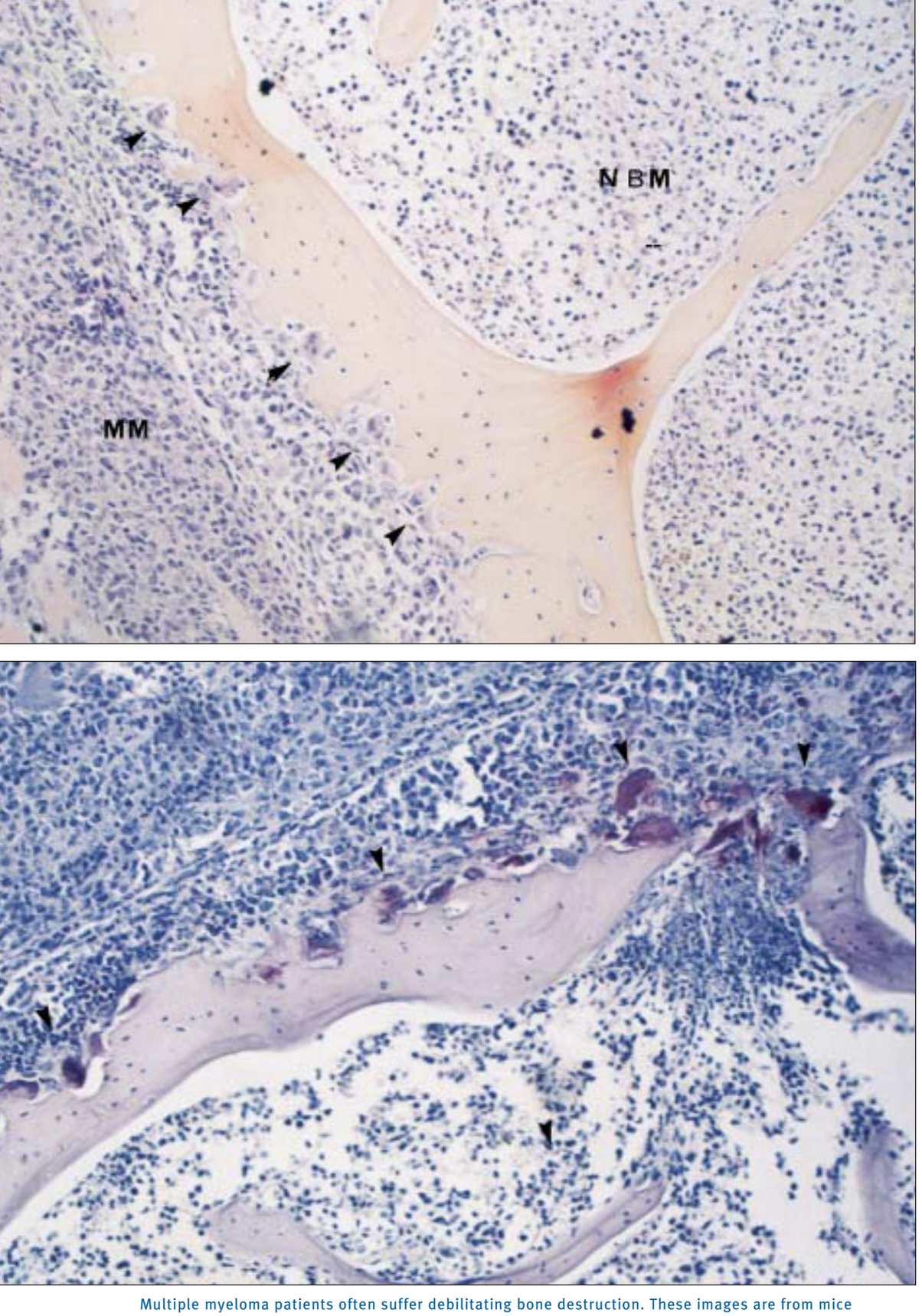


Myeloma Research Foundation, and the Department of Veterans Affairs. When he met Mundy, Roodman may not have known much about bone, but he did know a lot about cell differentiation, and he was having success developing difficult cell cultures.

Mundy had been asking around, looking for someone who could help him culture cat bone marrow, and he heard about Roodman. Roodman knew that sheep marrow had been cultured, and figured, *Sure, we can do cats.* The two teamed up. They succeeded with culturing bone marrow from cats, and then went on to make human- and mouse-marrow cultures, along with cultures from baboons. Before Roodman and Mundy got started, people had cultured bone marrow, but those cultures didn't form a key ingredient—osteoclasts.

Using Roodman's techniques, you could take bone marrow from sick patients and grow it in the lab. This meant researchers could study diseased osteoclasts up close and

Roodman has been able to minimize multiple myeloma bone disease in mice. The lower images have fewer myeloma cells and less bone destruction. Roodman used a treatment in these cases that targets a protein called MIP-1 alpha. The bone sections shown on top were not treated and show bone degeneration and myeloma cells. Arrows point to osteoclasts.



Multiple myeloma patients often suffer debilitating bone destruction. These images are from mice injected with human multiple myeloma. TOP: Osteoclasts near the multiple myeloma cells pit bone (see area marked "MM") while the osteoclasts near normal bone marrow don't (see area marked "NBM"). BOTTOM: Arrows point to stained osteoclasts that resorb bone.

over time. They could also manipulate the cells and experiment on them in ways that were impossible in living patients.

"Up until that time, they had been very hard cells to study," Mundy says. "Most people around the world use the technique he developed or techniques derived from it."

Roodman is more modest about his achievement. He considers his meeting Mundy a serendipitous event that shaped his career.

After he cultured osteoclasts in the early '80s, Roodman turned his attention to diseases that involved the cells. He used the new culture techniques to study the bone disease wrought by an aggressive adult hematologic cancer called multiple myeloma. Like leukemia, multiple myeloma is a cancer of the blood. Specifically, it's a cancer of the plasma cells. If plasma cells become cancerous, they congregate in bone marrow, crowding out normal marrow cells that would produce red and white blood cells as well as blood-clotting platelets. Sometimes the myeloma cells form tumors.

Before chemotherapy, the life expectancy for someone with multiple myeloma was dismal, an average of seven months after diagnosis. Today, with treatment, the average has increased to around three years, and patients strong enough to get stem-cell transplants live, on average, five to seven years.

Much of the pain patients experience results not from the tumors, but from the cancer cells' interaction with osteoclasts. The cancer cells stimulate nearby osteoclasts, causing them to alter the bone. As the disease progresses, the bones ache terribly, eventually becoming deformed and unbelievably fragile. "Myeloma patients can fracture a humerus by closing a car door," says Roodman.

He has delved into the question of what causes this bone destruction. And now he is pinpointing the factors that drive the osteoclast frenzy; his results may also shed

ALSINA, M., BOYCE, B., DEVLIN, R.D., ANDERSON, J.L., CRAIG, F., MUNDY, G.R., ROODMAN, G.D., DEVELOPMENT OF AN IN VIVO MODEL OF HUMAN MULTIPLE MYELOMA BONE DISEASE. *BLOOD* 1996;87:1495-1501. COPYRIGHT AMERICAN SOCIETY OF HEMATOLOGY; USED WITH PERMISSION.

light on the cancer itself.

In cases of myeloma, the osteoclasts themselves are normal—unlike in Paget's disease, where there are simply way too many of the cells working way too hard. Drugs exist that can inhibit osteoclast activity. Unfortunately, they inhibit all the osteoclasts in the body. Since myeloma cells only affect nearby osteoclasts, this approach is less than ideal. After all, osteoclasts are essential to the maintenance of healthy bones.

So how do myeloma cells trigger the nearby bone disease? Roodman has identified a protein that may be myeloma's messenger to the osteoclasts, macrophage inflammatory protein–1 alpha, or MIP-1 alpha for short. If he's right, his research raises the possibility of targeted treatments that would only affect the diseased regions.

Bill Bensinger, a professor at the Fred Hutchinson Cancer Research Center in Seattle, says Roodman worked for years without great recognition in the field, but that's now changing as researchers realize that his work is providing keys to understanding how bone disease operates. (Roodman's CV includes pages of impressive awards and positions, including service on national advisory groups, the board of the Paget's Foundation, and the editorial board of *The Journal of Clinical Investigation*.)

Bensinger is encouraged by the prospects for improved treatment of myeloma bone disease coming out of Roodman's lab:

"He's honing in on several new pathways that I think have been unrecognized. Once you understand the signals, you can disrupt that pathway."

A couple of years ago, when Roodman was deciding if he should come to Pitt, he was being courted by four other major research centers. And when he came to Pitt in 2001, his entire lab agreed to join him. Now that he's here, Roodman is studying the effects of MIP-1 alpha in mice that have modified immune systems and have been inbred to be genetically identical. These mice let researchers test one factor, in this case MIP-1 alpha, without worrying about teasing out other influences, like genetic variability. So far, the results are positive. When Roodman injected the mice with human multiple myeloma cells, they developed such severe bone disease the myelomas impinged on the spine and they became paraplegic. When he injected the mice with human myeloma cells but blocked MIP-1 alpha activity, the mice didn't get bone disease, and they also ended up with fewer tumors. He hopes the research will lead to clinical trials in the next few years.

Like myeloma bone disease, Paget's is a condition whose root cause has eluded scientists, even as treatments have improved. It's clear that the osteoclasts in Paget's patients are diseased; they are abnormally large and have as many as 100 nuclei. (Normal osteoclasts have perhaps two to four nuclei.) These osteoclasts also respond to extremely low levels of hormones, which throw off the mechanisms the body would normally use to regulate these cells. What's been less clear is how the osteoclasts get that way. This is a question that's driven the other main branch of Roodman's work.

Fred Singer, a nationally recognized leader in the treatment of Paget's, studies the disease at the John Wayne Cancer Institute in San Diego, even though Paget's isn't a cancer. Singer is painfully aware of how little information doctors used to have about Paget's; he has done clinical research and treated Paget's patients for 30 years. About a decade ago, Singer got a call from then-stranger Roodman, who was at San Antonio at the time. Roodman said he'd been working on aspirated bone marrow cultures and was wondering if Singer wanted to collaborate on Paget's research. Singer said yes, and the two have been working together since.

"It's been one of the most fruitful relationships I've ever had, short of my wife," said Singer. "I think it's no understatement to say that he's been the single most important person in the field in understanding this disease."

It seems most likely that, like many cancers, Paget's results from a confluence of factors. The disease clearly runs in families. Kenneth Halstead has two brothers with it, and his mother was diagnosed with Paget's at the age of 101. Ten to twenty percent of patients have a relative with the disease. Today, most doctors accept that Paget's is probably caused by a combination of genetics and environmental influences.

Roodman has been trying to decipher what the environmental factors are. He thinks that a viral infection is key in causing Paget's in genetically susceptible people. The culprit? Roodman suspects the virus may be the same one that causes measles. The circumstantial evidence is enough to push his research forward, but Roodman tempers his excitement with disclaimers, stressing that he hasn't proved the link.

Yet Roodman is not the only one excited about the possibility.

"The fat lady hasn't sung yet… [but] I think he's right," says Mundy.

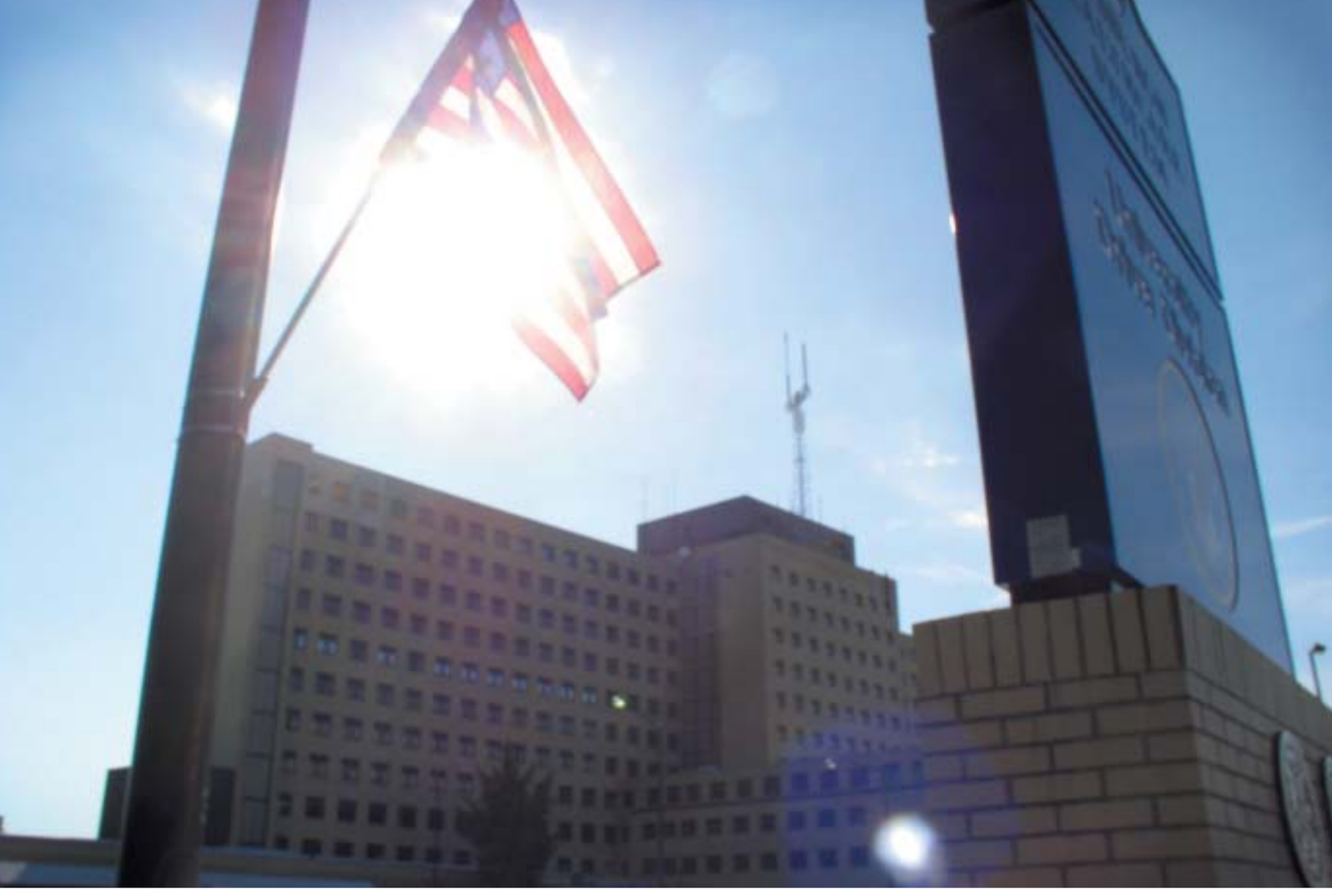
Others, including Singer, think so too, but they agree that it's still an open debate.

What Roodman has discovered is evidence of viral transcription in the osteoclasts of Paget's sufferers. Essentially, the transcription evidence is like a calling card, showing that the virus has been there and been active. Of course, not everyone who gets measles gets Paget's, but it could be that measles is a trigger in susceptible people. Because the measles vaccine is now widely used, Paget's could become much less common in the future.

One doctor told him Paget's must have been described on the last page of the textbook, the page he didn't read. He was also told that doctors used to diagnose the disease only after patients' heads grew so big their hats no longer fit.

But many must live with it today. Every year, Paget's patient Halstead is invited to talk to a new crop of medical students and others at Duke University to help them understand the disease that has so shaped his life. He says when he started years ago, one doctor told him Paget's must have been described on the last page of the textbook, the page he didn't read. He was also told that doctors used to diagnose the disease only after patients' heads grew so big their hats no longer fit. (Halstead outgrew his hats.) Though a cure wouldn't undo the damage to his body, Halstead would like to see it available to others. He himself has benefited from treatment advances through the years. The new drugs have provided relief from the constant pain; and, he notes, with treatments now available, people diagnosed today could avoid the level of bone degeneration he has suffered.

Fortunately, his children show no signs of Paget's so far. But they get tested regularly. With four cases in the family, it's a possibility that's always out there lurking. ■



SOLDIERING ON

UNSUNG HEROES

BY EDWIN KIESTER JR.

When the story of University of Pittsburgh medical education and research is written, two capital letters will leap off the page: VA. The U.S. Department of Veterans Affairs is a largely unsung and often unrecognized major player in Pitt physician education and research. More than half of Pitt's medical school graduates spend time during their rotations tending to patients in one of three VA Pittsburgh Healthcare System hospitals. Some $24.5 million in Pitt research is at least partially funded by the VA, and more than 200 faculty members hold joint Pitt-VA appointments.

"Very definitely, people don't understand the importance of the VA in promoting basic scientific research," says Peter Strick, professor of neurobiology and codirector of the Center for the Neural Basis of Cognition, a partnership with Carnegie Mellon University. Strick is a VA senior career research scientist in addition to his university affiliations; up to one-third of the support for

his laboratory and its much-admired work in mapping previously unrecognized communication between brain centers is underwritten by the VA. Strick cites the little-known key contributions of VA scientists to basic research, noting in particular the 1977 Nobel Prize to Rosalyn Yalow of the Bronx VA Medical Center for developing the radioimmunoassay test.

The East Side New York girl decided early on that she wanted to be a physicist; and as a young woman, she was further inspired by Madame Curie's biography. But in 1941 it seemed unlikely that good graduate schools would accept or offer financial support to a woman. She graduated with high honors from the then all-female Hunter College, yet the only semiscientific job she could get was as a part-time secretary to a biochemistry professor—she could type and agreed to take stenography courses. She eventually filled an opening as a graduate assistant taking classes and teaching physics at the University of Illinois (where she was the only woman among 399 men and where, upon receiving three A's in her coursework and an A-minus for lab work, she was told the A-minus confirms that "women do not do well at laboratory work").

When the war ended she returned to New York and there found that the VA was more accepting of female researchers. She stayed at the unheralded Bronx Center for 30 years, where she could pursue her fascination with radioactivity. The radioimmunoassay was developed in 1959, and since has become the key test routinely used to trace hundreds of substances circulating in the blood, from insulin to peptide hormones. Yalow's work has been a boon to diagnosticians worldwide.

Students report they find the VA welcoming as well. For one thing, VA patients seem particularly open to interacting with med students, notes Michael Jude Rest (Class of '04). Last year, Rest spent three weeks of his medical rotation at the VA center on University Drive, then returned for six weeks of surgery rotation. "I got to see all sides of patient care," he says of his VA training. "I brought patients to x rays and scans and talked directly to the radiologist. I went to pathology labs and actually looked through the scope with the pathologist. I went to the microlab and Gram-stained cultures and studied the slides with the microbiologist. Nowhere else do these opportunities present for a junior medical student."

Apart from the VA's impact on individual lives like Yalow's and Rest's, statistics on the VA and health care are impressive, to say the least. The VA's 163 medical centers constitute the nation's largest network of care facilities. The congressional appropriation for VA research in 2002 amounted to $400 million. Leveraged with National Institutes of Health (NIH) and other grants, its funding adds up to a cool $1.4 billion, spread over 10,000 VA projects involving 3,000 investigators. In addition to Yalow's, VA researchers have won two other Nobels and six Lasker awards. Indeed, Pitt's transplant trailblazer Thomas Starzl got his start under the VA tent. Starzl's initial animal studies that led to human organ transplants were conducted at the VA medical centers in Denver and Chicago.

The VA impact on training is equally impressive, with 81,000 healthcare professionals getting their feet wet at the VA every year. Frederick DeRubertis, Pitt professor of medicine and chief of medicine for the VA, sees VA training as critically important both to future patient care and to medical research. He speaks of a growing need for physicians trained to bridge the gap between basic science questions and clinical medicine.

"The clinician-scientist has become an endangered species," adds Steve Graham, the VA's associate chief of staff for research and a Pitt professor of neurology. "The VA provides an environment where the physician-scientist can prosper. VA training, with its close exposure to patients, develops a cadre of physicians who see, firsthand, patient needs and whose research interests grow out of the problems they encounter at bedside." The VA boasts plenty of great MDs who explore underlying basic questions of physiology (like Pitt's David Roodman, profiled in this issue, and John Hibbs, MD '62, of nitric oxide fame at the University of Utah). Yet the VA also is a place where researchers are encouraged to look at immediate matters of improving patient care. Pitt's Strick notes, also, that VA-trained MDs and PhDs work closely together. Neurobiologists with an intricate knowledge of brain anatomy stand at the neurosurgeon's elbow to guide the deep-brain stimulation now used to treat Parkinson's disease and other movement disorders; a minuscule error in placement can make the treatment futile—or worse.

The exact roots of Pitt-VA (and, indeed, of VA-auspices) research appear lost to history. During the 1920s and 1930s, doctors at VA hospitals informally, and often out of their own pockets, carried on clinical research projects on veteran-related problems that intrigued them, like the respiratory disorders produced by poison gas in World War I. Some of this informal research was conducted at the Aspinwall Hospital (now the H.J. Heinz III Progressive Care Center) by physicians affiliated with the School of Medicine. After World War II, their work and that of others led to a more successful treatment for tuberculosis, at a time when 10,000 veterans were being treated for TB in VA hospitals nationally. VA post-World War II work also revolutionized and standardized prostheses and rehabilitation methods. The VA finally received its first official congressional appropriation for research in 1958, of $9.3 million, and Pitt was an early beneficiary. The relationship has burgeoned since. Besides the $24.5 million in faculty research the VA sponsors with the University, it also coordinates a $17 million, multicenter trial in the treatment of acute renal failure that is jointly funded by the VA and NIH.

She graduated with high honors, yet the only semi-scientific job she could get was as a part-time secretary to a biochemistry professor—she could type.

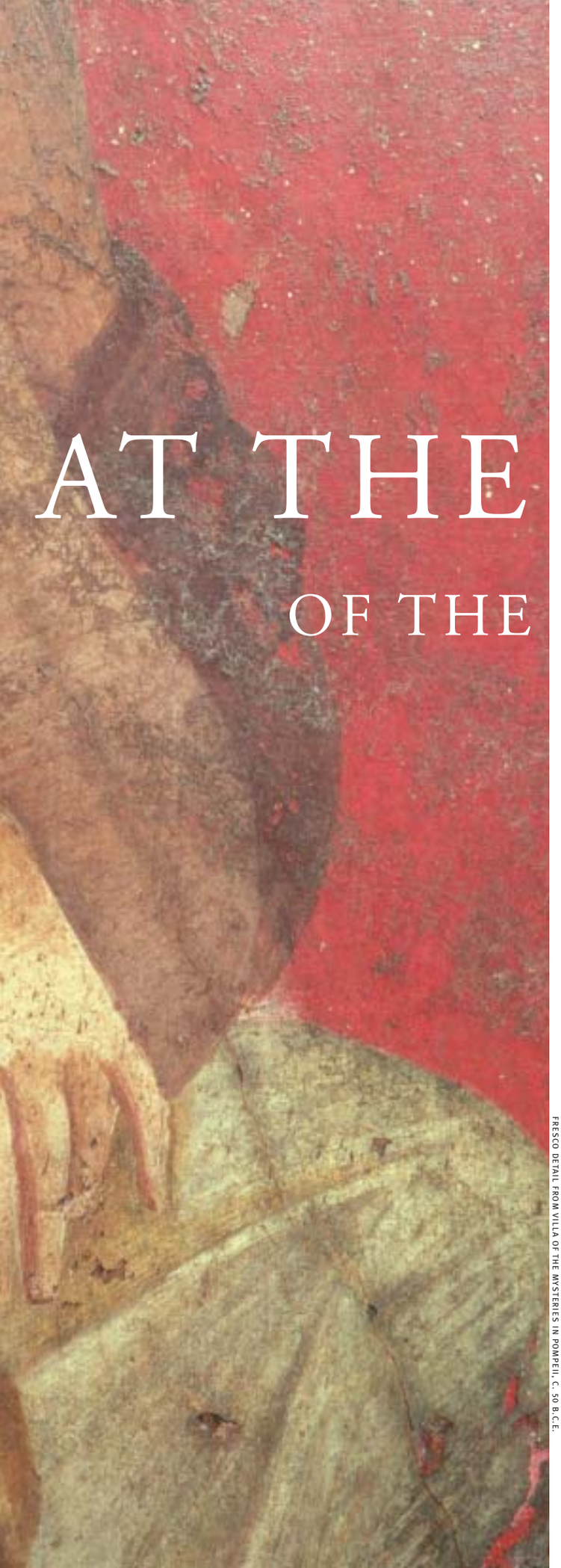
Pitt has another VA distinction. It lays claim to four Centers of Excellence, one of only two institutions nationally with more than two. Centers of Excellence are collaboratives established by the VA in which specialists from several disciplines are brought together. Pitt's centers are the Geriatric Research Education and Clinical Center, Rehabilitation Research and Development Center, Mental Illness Research Education and Clinical Center, and the Center for Health Equity Research and Promotion.

"Pittsburgh is one of our premier research programs," declares Nelda Wray, the VA's chief national officer for research. "It has a long history of achievement that continues today. We place great value on the relationship between the VA and the University." ■

CAMI MESA



We know that if we can improve communication between doctors and patients, patients will do better. A new institute at Pitt is dedicated to the subtler elements of the clinical encounter.



FRESCO DETAIL FROM VILLA OF THE MYSTERIES IN POMPEII, C. 50 B.C.E.

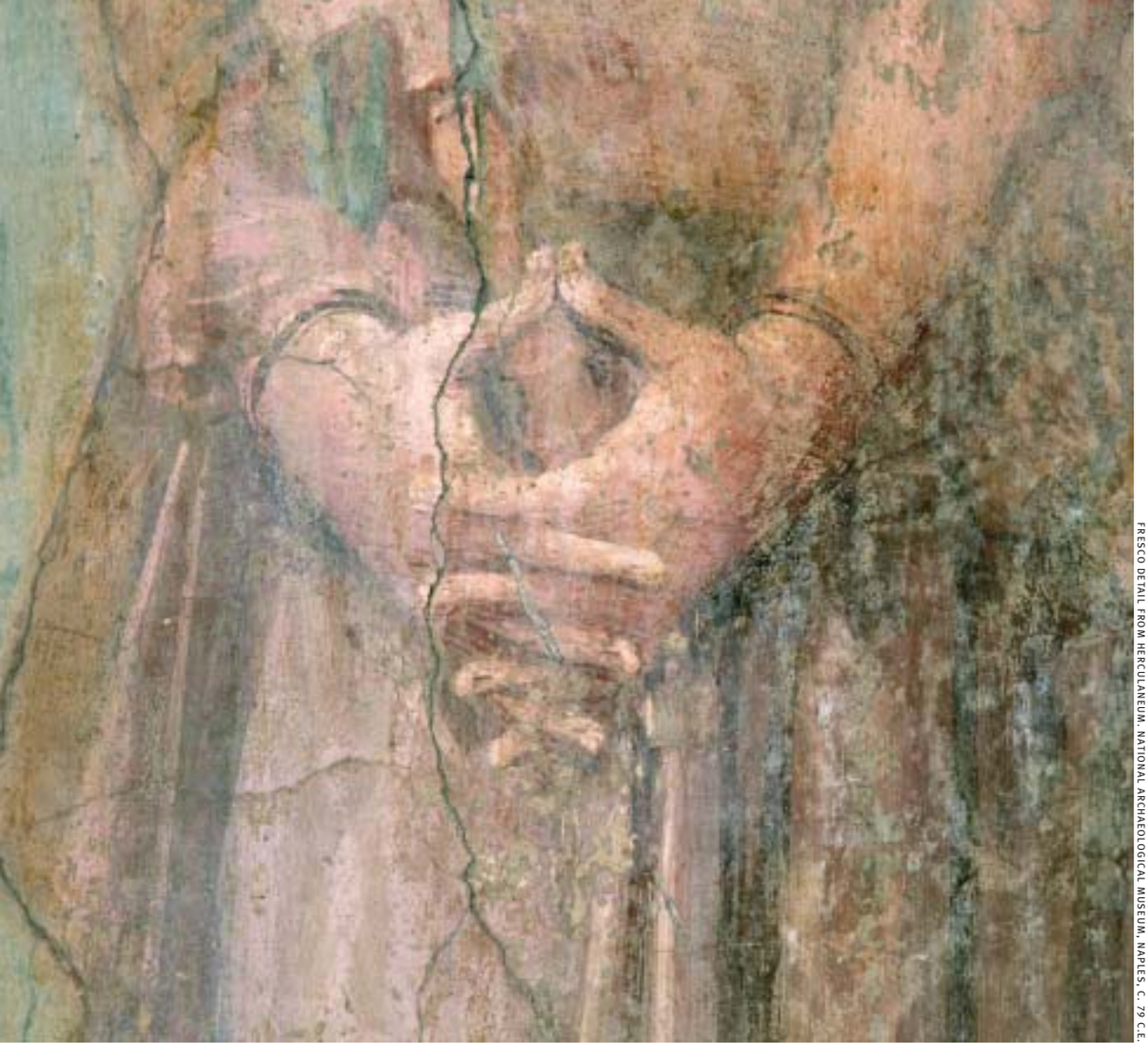
WHAT'S SAID, WHAT'S NOT SAID, WHAT SHOULD BE SAID | BY DOTTIE HORN

AT THE HEART OF THE CLINICAL ENCOUNTER

Chemotherapy had done little to help John Colby (not his real name), a 23-year-old with leukemia. Doctors recommended a bone marrow transplant and began preparations, which would take three or four weeks, for the procedure.

Then, suddenly, Colby came down with pneumonia. Because his immune system had been destroyed by the leukemia, he had no defenses against the infection. Hitendra Patel, a University of Pittsburgh Cancer Institute hematology and oncology fellow, admitted Colby to the hospital and gave him the most powerful antibiotics known. Even so, within a week, Colby's lungs failed. He was placed on a ventilator, which meant that he had to be sedated and was unconscious. His parents,

PHOTOGRAPHY | MIMMO JODICE, CORBIS



FRESCO DETAIL FROM HERCULANEUM. NATIONAL ARCHAEOLOGICAL MUSEUM, NAPLES. C. 79 C.E.

always by his side, were optimistic—the pneumonia had come out of the blue, and they hoped that the transplant would be successful. Every day, Patel updated them about changes he was making to their son's antibiotics (new drug-resistant microorganisms were often found in Colby's lung secretions). But there were other issues to discuss, and Patel struggled to find the words.

The parents were so devoted to their son and so hopeful. How could he help them understand that this would likely be the end of their son's life? When should they give up hope of any recovery and take him off the ventilator?

Patel spoke to the parents every day, explaining the gravity of the situation. Eventually, the parents made the decision to take Colby off the ventilator. The day after they removed the ventilator, Colby died.

Patel wanted to be better prepared for conversations like the ones with the Colby family, which he'd always found difficult and uncomfortable. When he saw a notice about a program to help oncology fellows improve their communication skills, he decided to apply.

Patel was accepted to the program and, in April 2002, traveled to Colorado to participate. Every day during the weeklong workshop, Patel would practice his skills with several other fellows: In front of the entire group, he would go through a clinical interaction with a "simulated patient"—a trained actor. One day, his job was to tell a patient that she had liver cancer and to negotiate a treatment plan. The next day, he would see the same patient to tell her that the treatment wasn't working—there was nothing more doctors could do to stop or slow the progress of her disease. During each daily role-playing session, Patel received comments from the group about what he did well and what he might change. "That's when I realized that I can handle things differently," says Patel.

Since completing the training, Patel has incorporated many of its techniques into his conversations with patients and their families. He has learned, for example, how to handle emotions and nonmedical concerns. Say a patient is worried about what will happen to his wife after he dies. Patel lets the patient know that he recognizes and understands the concern; he has discovered that very simple gestures, like saying, *I see that you are concerned about your wife*, can open the door for the patient to talk further. He tries to present options. *We can talk to our social worker about that,* he might say. Or, *People sometimes discuss those kinds of issues in our support group.* Offering an outlet for patients to express their feelings or worries makes the medical encounter more fulfilling and helps them cope with painful emotions, Patel has learned.

Research suggests that doctors of all kinds may want to look at their communication skills. A recent study surveyed 755 "sicker" adult Americans—those who either rated their health as fair or poor or who'd faced serious medical problems within the past two years. Half reported that their regular doctors do not ask for their ideas and opinions about treatment and care. Half indicated that, over the past two years, the doctor had not discussed with them the emotional burden of coping with the condition. A third said they had left the doctor's office without getting important questions answered. (Researchers have been studying patient-physician communication since the early 80s—though Arthur S. Levine, Pitt's senior vice chancellor for health sciences and School of Medicine dean, was ahead of the times. He published a 1973 article in *The New England Journal of Medicine* that looked at the effectiveness of a weekly teaching seminar to help oncology fellows cope with their reactions to dying patients.)

The training Patel attended in Colorado was part of a National Cancer Institute–funded research project for which Robert Arnold, professor of medicine at the University of Pittsburgh School of Medicine, serves as coprincipal investigator. Throughout the next five years, Arnold and his collaborators will train 180 oncology fellows; their goal is to see whether the course actually improves the fellows' ability to talk to patients and families about end-of-life issues. Fellows are evaluated at the

beginning and at the end of the weeklong course to measure changes in their interactions. (It is still too early to draw any conclusions from the data.)

The oncology fellows project is part of a larger effort by Arnold, and by the University of Pittsburgh, to study what happens at the heart of the clinical encounter: i.e., what's said, what's not said, and what should be said between a doctor and a patient. Researchers in scattered medical school departments have been studying such issues—but now, Pitt's recently formed Institute for Doctor-Patient Communication offers a supportive forum where interested researchers can meet monthly to discuss projects and share ideas. In addition, the institute will sponsor symposia and conferences; it will also reach out to medical students (see "Patient Interrupted").

"We know that if we can improve the interactions between doctors and patients, patients will do better," says Arnold.

He cites one study, in which researchers enrolled patients with diabetes who were placed randomly into two groups. Each study participant met with a research assistant for 20 minutes just prior to two regularly scheduled physician office visits. In the control group, the assistant provided standard education about diabetes; in the experimental group, the assistant taught the patients ways to become more involved in medical decision making. At the third visit, the experimental group showed better diabetes control (lower blood glucose levels) and fewer functional limitations than the control group. A similar study has shown that training hypertensive patients to communicate with their doctors can also lead to lower hypertension.

Such evidence suggests that better communication may equal better health—yet the doctor-patient interaction is fraught with the potential to become "chaos," says Bruce Ling, a Pitt assistant professor of medicine and codirector for research at the institute.

He describes the relationship as one that can break down at any number of points. Consider a typical office visit: "Mrs. Smith" comes in with an agenda and discusses her concerns. "Dr. Jones" takes in that information and begins to develop a treatment plan. At the same time, the doctor may come to the visit with certain goals—perhaps wanting to discuss health maintenance issues, like losing weight or stopping smoking. Dr. Jones must broach those issues and offer suggestions; Mrs. Smith must digest that information and respond. All in 15 minutes or less.

"If there is a misunderstanding anywhere in that exchange," says Ling, "that can really impact what happens after the visit—what the patient does and what the doctor does as well, in terms of ordering tests, using medicines, addressing needs."

And that's just what happens in a standard interaction. Consider a situation that requires more finesse. Imagine a patient who has spent hours researching obscure Internet sites and has learned of a new wonder drug for arthritis available from a nutritional supplement provider. The patient is adamant that this drug will be a cure-all. If the doctor does not agree with the patient's thinking, the relationship can quickly become adversarial, notes Ling: "It takes some very good communication skills to be able to address the [patient's] information without making it look like you're just blowing it off and without offending the patient."

To add to the challenge, there is, of course, often conflicting evidence within medicine and uncertainty among physicians about how to manage some conditions. This ambiguity can complicate the doctor's role. First, the doctor must highlight what the controversies are in a time-efficient manner *and* in a way that the patient can understand. The doctor then needs to let the patient form and express an opinion and to work with the patient to develop a treatment plan. "That can be very difficult," says Ling.

He remembers a clinical encounter in which he wanted a patient to be screened for colon cancer. There are several different tests that can be used for the screening. "Current recommendations are that we speak with the patient, go over each of the options, and work with the patient to come up with the option that the patient accepts, prefers, and that we feel would be appropriate," says Ling. In this case, however, the patient didn't understand much of what Ling was saying. "I spent 20 minutes going over this," he says, "and I think afterwards the patient was more confused about

PATIENT INTERRUPTED

The third-year med student is eager to practice taking a history. He enters an exam room and greets the patient inside. She came to the doctor, he learns, because of two weeks of sharp shoulder pain. He asks about her living situation; she is married and has two toddler sons. He decides to ask some screening questions.

"Have you ever been physically abused by your partner?" he asks. She looks up at him.

"Yes."

The student is speechless. No patient has ever before answered yes when he asked that question.

"It's pretty intimidating to the student the first time that happens," says Melissa McNeil, professor of medicine. In the Clinical Skills course for second-year students, McNeil teaches students how to handle such a situation. "We give them some statements that will help them move to the next part of the encounter, so they're not left feeling uncomfortable, nor is the patient," says McNeil.

In her course, McNeil teaches students how to talk with patients about other potentially sensitive issues, including sexuality, alcohol, and drug abuse. Once the course is over, students move on to third-year clinical rotations. Depending on their priorities, clinical faculty members may or may not reinforce the communication skills students have learned.

The medical school's new Institute for Doctor-Patient Communication has an eye on ensuring that Pitt med students have the training and practice opportunities they need to become capable communicators. The just-formed institute is mapping out a strategy, guided by Laurel Milberg, adjunct clinical associate professor of family medicine and institute codirector for education.

"We want to provide resources and support to improve education in doctor-patient communication skills across all four years of the medical school curriculum," says Milberg.

She is first canvassing to see which courses and clinical rotations currently include instruction on relating to patients. Eventually, the institute will partner with professors who want to incorporate communication—or more of it—into their courses or rotations and will develop ways to support those professors.

Institute organizers would also like to see med students be more extensively tested on their patient one-on-ones during simulated clinical settings.

Studies show that when a doctor initiates discussion with a patient (usually by asking why the patient came in), the doctor listens to the patient's opening statement for an average of just 11 to 18 seconds before interrupting. Research also tells us that patients usually don't share their most significant concern first, but initially talk about less important issues. If physicians interrupt, they may never hear what's really on the patient's mind, says Milberg. She intends to help future Pitt med grads get the whole story. —*DH*

what colon cancer screening is all about." He fears he put up a new barrier for the patient and made it less likely the screening would ever take place.

Situations like this led Ling to wonder about the best way to approach the topic. "Maybe I shouldn't expect the patient to be able to grasp these very complex issues and make that decision right then and there," says Ling. "Maybe it's that you send written material and prime the pump and prepare the patient for such a discussion." Now, with the support of a Career Development Award from the National Cancer Institute, Ling plans to identify successful techniques for relaying colon cancer screening information. He'll also identify common pitfalls.

The doctor-patient interaction is fraught with the potential to become "chaos." The relationship can break down at any number of points.

Ling is hoping to find answers to some burning questions: Are there certain things that are either said or done that predict whether one ends up getting screened? What might a physician say or do that results in increased trust and satisfaction? And if trust and satisfaction are high, does that make a difference in whether the patient decides to get the screening?

Asking such questions could save lives. Research shows that only 40 percent of Americans are up to date with their colon cancer screening. "We are hoping to change [that statistic]," says Ling, "so that we have a majority of the population who are up to date, so that they can benefit maximally from the technology that is out there."

The patient was fidgeting and looked like she was about to burst into tears. She had received a card in the mail telling her that her Pap test was abnormal—and that she might have cancerous or precancerous cells. Judy Chang, then an undergraduate who volunteered at a clinic, spoke with the woman when she came in for further evaluation. Chang explained what the abnormal Pap test meant and what to expect during the exam. As she spoke, the woman's face relaxed and she stopped fidgeting. It was a scenario Chang witnessed repeatedly.

"Just providing that information seemed to change their entire outlook on the procedure and maybe even on how much control they felt like they had over their health," says Chang, looking back. "It was striking how that interaction, though it was very short, could actually be very powerful." The undergraduate liberal arts major decided to become an MD—and eventually she decided to study how doctors communicate with patients.

Chang has studied interactions physicians have with patients who've experienced domestic abuse. Now, as an assistant professor of obstetrics, gynecology, and reproductive sciences at Pitt, she is planning a broader study. Chang will look at how physicians talk with patients during obstetric visits about factors that can negatively affect health—such as drug and alcohol use, smoking, multiple sex partners, and domestic violence. Like many others who study physician communication, she will tape-record and analyze the conversation between the doctor and the patient. Yet, as she plans the project, she faces many challenges inherent in this type of research.

First, doctors—as well as patients—have to agree to participate in the study and to have their interactions audiotaped (some researchers even use videotapes, so that they can observe nonverbal communication). Researchers wonder whether the self-selected group that elects to take part is representative. "Are they better communicators in the first place, or at least more confident about their communication skills, so that they're willing to participate in the project?" asks Chang. She also worries that doctors, conscious of being in the spotlight, may change the way they interact with patients when they know they're being recorded—bringing up the old research quandary of potentially changing something just by watching it. "You don't know really if it reflects reality when you're audiotaping," says Chang.

Once she has taped the conversations, Chang will have to decide how to analyze them. Some researchers boil the conversations down to sets of phrases or sentences: What's being said? Is it medical information or psychosocial talk? Is the doctor or patient speaking? Other researchers focus more on the back and forth. Who starts the conversation and how? Do the two parties take turns? Are there lots of interruptions? Do people pick up on each other's cues—or do they not pick up on cues?

Still others focus on the tone of the conversation. They take an audiotape and blur the words, so that a listener cannot discern the content of the conversation but can still hear the cadence and volume of the speech. Then they'll have a group of people (who have no connection to the conversations) listen to the tapes and categorize the general tone of the healthcare provider—was it aggressive, for example, or soothing?

As she refines the methodology of her project, Chang is looking forward to the opportunities offered by the new institute: "For me as a junior investigator, someone who's just starting out in this field, I'll now have a resource to learn from other people's experience as well as a forum. I can bounce my ideas and plans off of people who are also thinking about the same issues."

But there are a few big "what ifs" involved in such efforts. What if Patel, who sought out help, is an exception? What if, after researchers carefully plot out ways to enhance clinical encounters, Arnold and his colleagues find physicians aren't motivated to learn new techniques? What if the attitude is, "Who has the time for this?" It's not just a matter of teaching old dogs new tricks to ask physicians with notoriously busy schedules to spend time bettering their one-on-one encounters.

"It's hard for physicians to take two to five days and go someplace and spend eight hours a day focusing on their communication skills," says Arnold. "A lot of physicians won't do it."

So the mountain may come to them. Arnold is looking into less time-consuming and simpler ways for doctors to get feedback. With his collaborators at Duke University, he will experiment with giving feedback on a CD to oncologists who send in tapes of patient sessions. Then the researchers will have the oncologists tape their visits again.

Arnold believes that, as new communication techniques and teaching methods are developed, more and more doctors will invest the time to improve their skills.

"In my experience, practicing physicians are *very* interested in doctor-patient communication," he says.

"They're interested in what they're having problems with. They get stuck and they're not sure what to do." ■





Jessica Lewis (left) and Jack Myers set the tone for Pitt to become a top-tier medical school.

BRICKER

FIRST FAMILY OF MEDICINE

EVERYTHING CHANGED WHEN THEY CAME TO TOWN

BY EDWIN KIESTER JR.

Children followed Jack Myers in curious droves as he walked around his neighborhood; for them he loved to identify rocks, trees, and animals they came across along the way. He is remembered as the consummate teacher. And at the University of Pittsburgh School of Medicine, where Myers was chair of the Department of Medicine from 1955 to 1970, throngs also trailed him, though those were often nervous retinues. After the "Morning Report," which kept many a resident awake the night before preparing, Myers would sweep through teaching-hospital wards examining patients while his house staff entourage stood by—usually trembling. The intern was to have the patient fully readied for Myers' examination: bed sheets turned back,





LEFT: 1970 *HIPPOCRATEAN*. RIGHT: COURTESY AMERICAN COLLEGE OF PHYSICIANS

Myers saw early on how computers could help physicians make diagnoses. He's shown here with Harry Pople Jr. of the Katz School faculty.

vital signs recorded, charts complete, and a med student would present the patient's history. Then, recalls Lawrence D. Ellis (MD '58), who served as an intern and resident under the late Myers and now is a Pitt professor of medicine, Myers would pepper the intern with clipped, sharp questions: "This patient is diagnosed with carcinoma of the lung, stage 4. How do you define stage 4? What medication is he receiving? How often? When was the last dose given?"

And to the student—"What are the possible causes of carcinoma of the lung? Who established that? What percentage of smokers develop carcinoma of the lung?"

"Woe unto the one who gave unsatisfactory answers, couldn't provide an answer, tried to evade the question, or offered an alibi," Ellis says. "Jack could accept errors or 'I don't know,' but he couldn't accept excuses. He had three rules—punctuality, attention to detail, and a commitment to excellence. And he was toughest on those he thought had the potential for excellence."

He wasn't known for patience, either. According to one possibly apocryphal story, Myers and his group once entered a room to find the patient with a full bedpan. Myers handed the bedpan to a man standing nearby. "Take this away," he said. "I'm in housekeeping," the man replied. "That's the nurses' job. That's not my job." Myers dumped the contents of the bedpan on the floor. "Now it's your job. Clean it up." And there's the tale of a resident who clearly bluffed when asked what level of oxygen supplement a patient was receiving. "Leave the bedside," Myers responded. There was no place on his staff for intellectual sloppiness—that's how you hurt patients.

"Oh, he was authoritarian," Ellis says. "He had uncompromising standards and insisted we all live up to them." Myers' strict code and no-nonsense training methods cultivated a cadre of dedicated physicians and revolutionized the school itself. Myers influenced the whole field of internal medicine and eventually helped bring it into the computer age. "He was an icon," declares Gerald Levey, who served as Pitt's chair of medicine and now is vice chancellor of medical sciences and dean of the David Geffen School of Medicine at UCLA.

"One of the great medical minds of the second half of the 20th century," continues Levey. "Four men essentially made Pitt a great medical center—Jack Myers, Hank Bahnson [former chair of surgery], Tom Detre [former senior vice chancellor], and Tom Starzl [of transplant fame]. But Jack Myers was first. He laid the groundwork."

Myers was also one-half of the medical school's most prestigious couple in those years. Jessica Lewis retired as an emeritus research professor of medicine. She founded the Hemophilia Center of Western Pennsylvania, which is affiliated with Pitt, and served as director of research and associate director of the Central Blood Bank. In hematology, she was also an icon, colleagues attest. Lewis' list of publications on blood coagulation alone runs to 17 pages and 217 entries.

There was nothing in Myers' appearance to account for the respect he commanded. "Just average in height and build," Lewis said in an interview a few months before her recent death. A fastidious, buttoned-up, coat-and-tie man, the former army medical corps lieutenant colonel wore a military crew cut to the end of his days, along with signature horn-rimmed eyeglasses. And his bedside teaching manner bordered on the brusque.

"He was the most honest, direct man I have ever known," says Thomas Piemme (MD '58), now retired as chair of computer medicine at George Washington University School of Medicine and Health Sciences. Unlike others who might try to soften bad news for patients, Piemme says, "He always gave everyone the full truth."

The Myers-Lewis team came to Pitt in 1955. They were part of a group headed by Eugene Stead (another legend in 20th century medicine), first at Emory University (where Stead rose to dean) and then at Duke University (where Stead was chair of medicine). Stead's group has been described as "the finest team of physicians, investigators, and teachers ever assembled in one place at one time." Most had moved together from Harvard University and Boston City Hospital, where Lewis and Myers met in 1946, when

Lewis was working in Harvard's Thorndike Memorial Laboratory. She was single, and she revealed decades later, "had been seeing different people, brokers, business people, a couple of surgeons. My colleagues said, 'Don't marry any of them. Wait until Jack Myers comes back [from the war]. You'll like him.' He came back, and I did." After a six-month courtship conducted in the corridors of Boston City Hospital, the two were married.

Myers' transfer to Pitt was something of a homecoming. He had been born in New Brighton, Pa., but the family moved to Arizona for his mother's health. He graduated from Stanford University and its medical school before moving east. At Pitt, Myers immediately set out to build a strong Department of Medicine. The medical school faculty then was part-time—staffed by private practitioners who taught their specialty a few hours a week. A first-rank medical school required a full-time faculty dedicated to teaching, Myers believed. He set out to recruit one.

"Leave the bedside," Myers responded. There was no place on his staff for intellectual sloppiness—that's how you hurt patients.

Albert B. Ferguson, Pitt's former longtime chair of orthopaedic surgery, had been an intern when Myers was a resident at the Peter Bent Brigham Hospital in Boston. He watched his friend's faculty makeover with amazement. "You would have thought he would have angered all the old part-time faculty who lost their positions," Ferguson says. "But Jack was so impressive with his vast knowledge that he won them completely over. He was a great teacher first and foremost, and they appreciated that. He changed a second-class institution into a first-class one." Myers' mentor, Stead, agrees: "Jack was one of the people who made Pittsburgh a great place."

Myers also established a formidable national reputation as a medical diagnostician.

"Physicians from all over the country contacted him about challenging cases that stumped them," UCLA's Levey says. "He could always provide the correct diagnosis." Myers spent 20 hours a week in the library reading medical journals, and, according to legend, remembered every word and every detail he read. "He had a photographic memory," Lewis said. "He never forgot anything he read." You could give him a topic—congestive heart failure, for instance—and he could immediately rattle off for an awed audience the latest information, often including journal titles and page references, a task that might have taken another physician days of library research. (Without looking it up, he also could report how many home runs Willie Stargell had hit in any given season. Myers committed to memory the batting averages of every Pittsburgh Pirate.)

Meanwhile, his reputation was spreading nationwide. In those days, physicians seeking certification by the American Board of Internal Medicine were required to take an oral examination before distinguished examiners, often at a patient's bedside. By his own estimate, Myers conducted as many as 2,000 "orals." His penetrating questions and insistence on precise detail made him a much-feared examiner. Myers also estimated that he rejected two out of three examinees, a record said to be the highest failure rate in ABIM history. For many other examiners, the failure rate was less than 20 percent. By then, Myers was known as "Black Jack."

Clark Sawin, a medical historian who is a professor of medicine at Boston and Tufts universities, did not draw Myers as an examiner—"But I had friends who went to the door of the examination room, saw Black Jack on the panel, and immediately turned around and rescheduled." Others, it is said, were so intimidated by Myers' questions that they vomited.

"Jack wanted straight answers," Piemme says. "Some people clearly didn't know, and they would invent an answer. He would let them go on until they hanged themselves." The dreaded orals have since been abandoned for a written, computerized examination.

Myers himself had aced his orals, his successor as interim chair in 1970, James Leonard, reported in recommending him for the Robert H. Williams Distinguished Chair of Medicine Award of the Association of Professors of Medicine (which Myers won). Myers applied for board certification while in Southampton, England, with the medical corps in 1944. The examiner handed Myers a heart patient's electrocardiogram and asked him to interpret it. Satisfied with the answer, the examiner then handed Myers a second tracing. "This is the same patient three days later," the examiner said. The young, uncertified Myers studied the ECG. "This is not the same patient three days later," he said confidently. "In fact, this is not the same patient at all." The examiner was caught off guard, according to Leonard; he had not recognized that the tracings came from different patients. He studied the ECGs again and acknowledged that the young man was right and deserving of certification.

The young Jessica Lewis was building her own record in the mysteries of blood coagulation. Eventually, her team's research at Pitt into how blood coagulates played a key role in Thomas Starzl's transplant breakthroughs. Starzl has been quoted as saying he doesn't think his work at Pitt would have gotten off the ground without her.

Lewis studied hemophilia, which had been the scourge of Queen Victoria's descendants and Europe's royal families in the 19th and early 20th centuries. Her interest dated from Boston City Hospital, where a young hemophiliac named Ted was an inpatient. People with "classic" hemophilia bleed freely from visible wounds but also internally from unseen injuries, the blood often pooling in joints or in organs and causing devastating damage. The only treatment in the 1940s was regular transfusions to replace the lost blood. "Ted would come down to my lab at all hours and talk to me," Lewis recalled. "He wanted a normal,



Warren Lewis headed the Mount Desert Biological Laboratory; later his son-in-law, Jack Myers, took over.

COURTESY MOUNT DESERT BIOLOGICAL LABORATORY

active life like any other young man, and he couldn't have it. It was sad."

In Pittsburgh, she quickly set up the hemophilia center. "She cornered the market in hemophiliacs in the tri-state area," says Frank Bontempo, medical director of the coagulation lab at Pittsburgh's Institute for Transfusion Medicine. The center was both a treatment and research center, but Lewis concentrated on research, which she saw as holding the answer for patients like Ted. Her lab work, and that of others, demonstrated that patients with hemophilia were genetically wired to have a lack or deficiency of one of several blood factors that promoted clotting. Their wounds, particularly internal wounds, did not heal normally. Today, gene therapies hold great promise for a cure, notes Margaret Ragni (MD '75), who directs the Hemophilia Center of Western Pennsylvania as well as hemophilia gene-transfer studies at Pitt.

Lewis came from a distinguished medical family. Her father, Warren Lewis of Johns Hopkins University, was an editor of *Gray's Anatomy*, and her mother, Margaret Reed Lewis, was the first to show the development of subcultures at 10-second intervals. The Lewis family spent summers at Salisbury Cove, on the Maine coast, where Warren Lewis headed the Mount Desert Biological Laboratory (a position which Myers later assumed). The family had built a summer home there in 1929. As a teenager, Jessica Lewis became interested in marine life, and set out to study the locally common dogfish shark, eventually focusing on its blood system. As described in her book, *Comparative Hemostasis in Vertebrates*, she continued and expanded upon that early research into blood properties for years. She took and analyzed blood samples from kangaroos, porpoises, and even an alligator. "Of course, I had help," she said. "Especially with the alligator."

Astoundingly, while compiling their record of professional achievement, Myers and Lewis also managed to parent five children. "Well, I always worked until I had labor pains, and the hospital was right nearby," Lewis said. "And I was usually back at work within 10 days. Fortunately, I had a wonderful woman to care for them." The oldest daughter, Judy, died in an auto accident in 1972. Three of the four others followed their parents into medicine and medical research.

She once swam across the entire chilly, one-mile bay.

They were stimulating parents. Daughter Elizabeth Myers is now an associate professor at Weill Medical College of Cornell University in New York City and a specialist in biomedical engineering. "When my mother had to go to the lab on weekends," Elizabeth Myers recalls, "she took me along, and I picked up her enthusiasm. I think my own interest in laboratory research dated from watching her and how dedicated she was to what she was doing."

Myers and Lewis commuted separately from their Allison Park home; he headed for the Morning Report and early rounds, she for her lab. They met at home at day's end for a martini (Lewis) and an "Iron" (Myers). They talked about the day, but seldom consulted each other on their projects. "We were both goers and getters, but our professional lives were quite different. I was a researcher. Jack was a teacher, a great teacher. That was his contribution. Most of our conversation was about events at the University."

The highlight of the household's year was the annual month at Salisbury Cove, where the family still gathers in August. "That is a wonderful memory for all of us," Elizabeth Myers says. "It was a time for relaxation and one-on-one talks." A small colony of summer homes populated by researchers' families grew up around the cove; Margaret and Jacy (Jessica) Myers both married sons of other Mount Desert researchers. Their father usually spent his "vacation" in the laboratory, but Lewis devoted herself to the family and outdoor pursuits. She once swam across the entire chilly, one-mile bay, "accompanied by a rowboat, of course," she said.

For all the intensity, it was a fun household. "Daddy was a big fan of the symphony; he never missed a performance, and at home he would play records and 'conduct' the orchestra," Elizabeth Myers recalls. He liked to sprinkle his talks with foreign phrases. He nicknamed the milkman "Monsieur DuLait." "For years, we thought his name was Mr. Dooley," Jacy Myers told a *Pittsburgh Post-Gazette* obituary writer on her father's death. Words and children were a source of pleasure for him: His children ate "bugs" instead of lobsters, "blubs" instead of blueberries, and "ronamacky" instead of macaroni.

At dinner, the family might play the River Game, which consisted of taking turns around the table naming rivers from A to Z. The kids knew about the Yangtze and Zambezi rivers well before any of their classmates. And every night, the children would have to report on what they had learned that day. "Nothing" was not an acceptable answer. They spent a lot of time looking things up in the *Encyclopedia*



COURTESY ELIZABETH MYERS

Lewis studied—and took—blood samples from porpoises, sharks, and alligators.

Britannica. And their mom made sure they saw the world. Jacy Myers remembers elevator races in Washington, D.C., and skinny-dipping in Bangkok.

Ragni, a Pitt professor of medicine, came to the Mount Desert lab as a Chatham College junior interested in medical research. "As soon as I walked into the lab and sniffed the air, I liked him," she says of Myers. "He smoked Marsh Wheeling stogies like my grandfather, whom I adored." Her experiences in the lab confirmed her interest in attending medical school.

While waiting for assays at Mount Desert, Ragni and Myers would sit on a bench overlooking the cove and listen to classical music broadcasts. They would play a game in which they had to identify the composer and the key the work was in.

In 1958, students voted to award Myers his first Golden Apple, given for outstanding teaching. That same year, Piemme wrote and directed the students' annual Scope and Scalpel: *Satan Place,* a spoof of *Damn Yankees,* featured Piemme in the role of Satan. He wore a devil costume with horns and with the unmistakable Myers crew cut and horn-rimmed glasses. Nobody enjoyed it more than Myers. "Jack thought it was uproarious," says Piemme. "Especially when Satan turned out to be the hero. Then he invited the whole cast to his place for drinks."

Indeed, the couple established a reputation as genial hosts, in Pittsburgh and at Salisbury Cove. Lewis, organized and logical, liked to schedule dinner parties on three consecutive nights—Friday for the house staff, Saturday for the neighbors, Sunday for colleagues. "Then you took out the dishes and silverware and got the house ready only once," she says.

In 1970, Black Jack became "Jack in the Box." He stepped down as chair of medicine with the distinction of University Professor and devoted himself to developing a computerized method of medical diagnosis. He teamed up with Harry Pople Jr., on the faculty at Pitt's business school, and Randolph Miller (MD '76), who is a professor of medicine and medical informatics at Vanderbilt University Medical School. Miller was a Pitt med student in the 1970s who'd been interested in computers since high school. By the time he was a resident, conversations with his professor turned into a collaboration:

"Jack very early saw the computer's potential for providing physicians with information that would help them in difficult diagnoses, but he didn't know much about computers. Harry Pople had computer expertise but not Jack's medical background. I could communicate with both of them, so I was the glue on the project. The goal was to build a knowledge-based tool physicians could use in the field. The collaboration lasted two decades."

The result of the collaboration was Internist I, the first computerized diagnostic database. Internist I later gave way to Quick Medical Reference, allowing physicians to interact and check their diagnostic decisions.

Failing eyesight eventually forced Myers to retire. Even then, he doggedly memorized journals, despite being forced to hold the reading material a few inches from his eyes. He died in 1998 at the age of 84. Lewis died this August during the family getaway in Maine; she was 86. Until then, she resided a few hundred feet off the Pitt campus, spending winters in Florida, but maintaining a lively interest in research.

Larry Ellis still keeps Myers' autographed photograph on his desk. He's not alone. Both Myers and Lewis are viewed with reverence today. Myers' influence on the quality and the reputation of the medical school, in particular, gave him prophetlike standing among those who knew, or knew of, him.

"He represented another glorious age," UCLA's Levey says. Myers himself never glorified the good old days; he led the campaign to eliminate the dreaded oral exam that had contributed to the Black Jack reputation.

"He said the whole system was a crapshoot," Ellis says. "The patient picked to be examined was a crapshoot; the examiner was a crapshoot. You might be failed by one examiner and passed with flying colors by another. A rigorous but uniform written exam graded by computer would be fairer and produce better physicians.

"Still," says Ellis, "there's no doubt that those of us who were exposed to his demanding standards became better physicians because of it. Jack Myers was absolutely the best bedside teacher of medicine who ever lived."

His wife, says Stead, was "a better scientist than Jack, which is no reflection on Jack. She was a better scientist than almost anyone." Together, the two, as Thomas Starzl noted recently, were for many years an indelible part of the fabric of Pittsburgh life. ■

MAKE YOURSELF AT HOME

PAULA DAVIS' EXTENDED FAMILY

BY JESSICA MESMAN



C.E. MITCHELL

"If you can drive in South Oakland, you can drive anywhere," a young admissions and financial aid counselor, Paula Davis, told her new colleague, Linda Berardi-Demo. They were in the department vehicle, and Berardi-Demo, who didn't have a driver's license and, more importantly, didn't know how to drive, was behind the wheel. (She did have a learner's permit.) At Davis' urging, Berardi-Demo turned the key in the ignition. Together they bucked down the skinny, swarmed streets of the lower Pitt campus, beginning a very important friendship.

This is how Davis works—the hard part first. She teaches herself, and if the task is daunting, she might ask a friend to help. This is how Davis, a 4-foot-10 woman who grew up in a housing project on Pittsburgh's North Side, who majored in English and got her master's degree in communications, who is not a clinician, an MD, or a PhD, became the assistant dean of minority affairs of the School of Medicine. On June 9, she became the first individual to win the Chancellor's Affirmative Action Award—which usually honors entire programs, not individual employees.

Davis has led the School of Medicine's efforts to enroll underrepresented minorities, boosting enrollment by 30 percent since 1994 among such groups as Mexican Americans, African Americans, and Puerto Ricans. And what's not been lost on students is how Davis and her staff offer academic grounding and even emotional support to help them achieve their goals. Davis' philosophy is to pull out all the stops: "Every question gets an answer. No one is ignored. No one is left behind."

The students who nominated Davis praised her for making the School of Medicine feel like home. For Davis, who did her undergrad and graduate work in the School of Arts and Sciences, it's only natural. "This campus has been my home since 1977," she says.

She describes the school as her family. Students have her home phone number; they're encouraged to use it. They send her Mother's Day cards. Berardi-Demo, now fully licensed to drive and the School of Medicine's director of admissions and financial aid, thinks of Paula as a sister. She calls Davis the consummate professional. Even in the muggy heat of summer, Davis is the one on the bus in the business suit, panty hose, and closed-toe high heels, not a bead of sweat on her smooth forehead. But Davis isn't *all* business—Berardi-Demo and she once pretended to be on the cast of *Les Miserables*. (That was when the two friends were out on the town in Boston.) And if you get Davis to talk about her children—Kathryn, 11, and Jason, 9, who has autism—she's likely to boast.

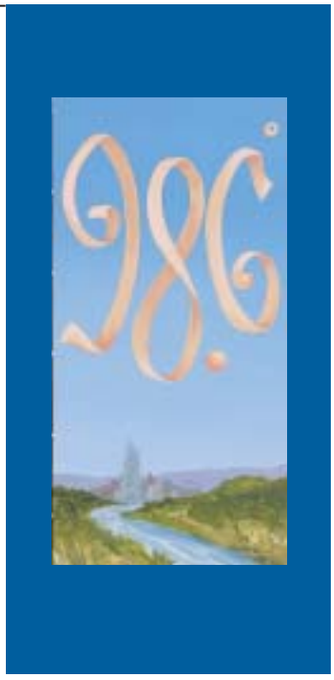
Asked if she knows the secret to Davis' success, Berardi-Demo responds, "Sagittarians need very little sleep." When pushed for a nonastrological explanation, she offers, "She doesn't believe in 'no.' I'd say, 'Paula, you better tell those people no,' but she just won't."

If you watch Davis at a table of aspiring students fresh from their first round of mock interviews for medical school admissions, you don't need anyone to tell you why she's held in such high regard. Davis is warm, responsive, and encouraging, even when doling out criticism. "You were nervous, huh?" she kids one young man who sighs, then laughs in response. Davis is an older sister who has all the answers. And there's nothing like watching the kids grow up. She's seen many of her recruits for the Medical Explorers program—which encourages minority students to pursue careers in medicine as early as high school—get their MDs from Pitt and begin practicing medicine in Pittsburgh. "Few things give me greater pleasure than to see our students grow from high school through their matriculation here," she says.

Berardi-Demo (whose own office has been lauded for its efforts at recruiting top-notch students) says that sometimes she and Paula wonder what they will be when they grow up. Davis says that in whatever incarnation, she will "keep fighting the good fight." One battle: Pitt is starting to lose top minority candidates to schools that can offer more funding; Davis has sounded the alarm for scholarship support.

"The composition of this country is changing as we speak," says Davis, who has pointed out before that patients in underrepresented populations are more likely to seek out doctors of the same ethnicity. "We must train a physician workforce that reflects our population," she continues. "This is a public health issue that we cannot ignore." ■

People and programs that keep the school healthy and vibrant



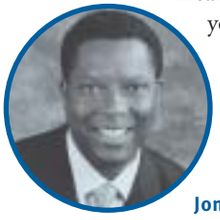
CENTER STAGE

NEW FOUNDATION MERGES SCHOOL AND UPMC EFFORTS

BY CHUCK STARESINIC

It's a long and winding career path that leads from the stage at Pittsburgh Public Theater to Pitt's School of Medicine. For Clyde Jones, the first big bend in that path came in the early days of the AIDS crisis, when he was a professional actor based in New York City. Working in the theater, he saw close friends and colleagues stricken with the frightening new disease and was moved to help. So Jones began garnering donations to ease the plight of those with AIDS.

He has been raising money for worthy causes ever since. And now, Jones will direct fund-raising efforts for Pitt's academic medical center—including the schools of the health sciences—through a new organization, the University of Pittsburgh and UPMC Medical and Health Sciences Foundation. The result of the new foundation, he says, will be an approach to fund-raising that is not fragmented, one that will meld together the clinical, research, and education aspects of medicine in the same way Pitt and UPMC do. It's not just a more efficient way to raise money, says Jones, it can also result in a more meaningful experience for donors. If you were interested in giving to neurology, for example, because you or a loved one had a neurological problem, your gift could be structured to simultaneously benefit top research, clinical care, and training.



Jones

Jones was most recently director of a similar development program for the Weill Medical College of Cornell University and New York–Presbyterian Hospital. But he has a special fondness for Western Pennsylvania—the place he left 20 years ago for college and career opportunities. He says he is thrilled to see that others are taking note of exciting developments in Pittsburgh, too:

"The School of Medicine in particular is seen around the country as a leader in medical education and research. And as its reputation grows there will be more people—not just in the region but around the country—who look to Pittsburgh, and look to Pitt, as a place to direct their philanthropy."

ASHORS GIVE STUDENTS A LIFT

THEY'VE PLANNED AHEAD

BY JENNIFER MATSON

Gilbert Ashor (MD '54) needed a lift to get to the School of Medicine every day. Fifty years later, he feels it's only right that he should get into the driver's seat and help someone else in need.

After classes, Ashor would hitch a ride from campus home to New Kensington. On a good day, he rode with a friend. On a bad day, he was dropped on Route 28 and had to foot the bridge over the Allegheny River. To pay for medical school, Ashor worked. For a while he delivered limestone and manganese to open-hearth feeders at the mill. At another point, he clocked in at the Alcoa plant, where he manipulated 1,800-degree Fahrenheit aluminum ingots with tongs. At other jobs, he was on the graveyard shift.

Ashor's schedule prepared him for the world of medicine (he took naps in the library whenever he had time). But now, he's making it easier for future med students to pay their bills. With his wife, Carol Ashor, he has made a planned gift of $750,000, endowing a full scholarship for students of high merit and limited financial means. A planned gift, often designated in a will, can be a great choice, Pitt's development officials note. They point out that donors can enjoy the gift in the present—whether it's real estate, artwork, or cash—while taking care of the University in the years to come. Planned gifts account for 15 to 18 percent of the University's funds, and as foundations cut back on giving due to poor stock portfolios, individual endowments are becoming more important.



The Ashors

At 73 years old, Ashor assists in heart surgeries every week at Santa Barbara Cottage Hospital in California, and he recently returned from Miraj, India, where he takes surgical teams to teach and operate. He shows no signs of slowing down, though he recently did so just long enough to see that the needs of his alma mater were met. ■

BOOSTER SHOTS

Oscar Marroquin, assistant professor of medicine, remembers the late Pitt cardiologist Galal Ziady as a superb clinician and teacher—extraordinarily humane, honest, and firm. When his widow, **Laila Ziady**, and others established the **Galal M. Ziady Award** for a fellow in cardiology, Marroquin was the first awardee. Asked how he resembles his mentor, Marroquin is characteristically humble: "I just try to be honest to myself and [my patients]." Sounds familiar.

For someone who wasn't a clinician, **A. Julio Martinez** saw an awful lot of patients. Neurosurgeons would call the Pitt pathologist into their operating rooms to diagnose tumors and other brain ailments so they could quickly decide how to proceed. Others sent him tissue samples from around the world. He had an unusually keen eye for distinguishing between very similar cells, and he was a leading authority on amoeba-borne brain infections. The Department of Pathology is creating a lectureship in memory of Martinez, a professor emeritus of neuropathology who died last December. The lectureship will allow distinguished experts in neuropathology to visit the school annually. *—CS & JM*

FOR MORE INFORMATION:

On the Martinez fund—Karen Weber at 412-647-7897 or weberkm@upmc.edu

For other gift opportunities—1-877-MED-ALUM.



CLASS NOTES

'40s

As a medical corps officer in the South Pacific during WWII, **Jack Brandt** (MD '43) was initially assigned to a hospital where he treated many soldiers who were obviously suffering—men confined to body casts or with missing limbs. The army sent Brandt to the island of New Caledonia then to Penrhyn Atoll, nine degrees south of the equator. There he was responsible for taking care of 11 men, all of whom remained healthy. It was great for the men, but it prevented Brandt from getting the intense training he thought he would get as an army doctor. When he returned to Pittsburgh, he applied for a residency at Children's Hospital of Pittsburgh, but all the positions were full. The Eye and Ear Institute had an opening, so he took an ophthalmology residency. A fluke became the best decision of his life. After having a private ophthalmology practice for the past 53 years, Brandt, who lived in Lock Haven, Pa., for the duration of his career, recently retired. He is splitting his time between Pennsylvania and Florida golf courses.

'50s

A friend leaving for vacation asked **Bob Eisler** (MD '55) if he would fill in as the psychiatrist at Mercer County Prison while he was gone. His friend's vacation ended after two weeks, but Eisler's tenure has lasted 23 years. Eisler has heard horror stories of how inmates used to get care. A colleague told him about a prison that had a wooden box filled with capsules and pills. When his colleague asked the guard what the box was, the guard replied it was medicine; if a prisoner was ill, the guards dispensed medication—almost at random. Fortunately, conditions like these have changed, yet there are still challenges in giving care. Eisler sits on a statewide committee to determine whether there is adequate communication between county jails and state prisons to ensure proper continuity of care.

'60s

Edith (MD '68) and **Tom Welty** (MD '69) volunteer with the Cameroon Baptist Convention Health Board in West Africa. Like many African nations, Cameroon struggles to control the spread of HIV and AIDS. The Weltys obtained a Call to Action Project grant from the Elizabeth Glaser Pediatric AIDS Foundation to work with the convention to reduce mother-to-child HIV/AIDS transmissions. The couple trains Cameroonians to counsel pregnant women. These counselors explain how expectant mothers can prevent spreading HIV, and the counselors urge the women to get tested for HIV and other sexually transmitted diseases. If the women agree to the tests, the workers use rapid-result methods, which allow the counselors to provide pre- and post-test counseling on site. From Boehringer Ingelheim Pharmaceuticals, the Weltys also secured a donation of nevirapine, an inexpensive HIV medication that prevents women from passing on the virus during childbirth. They developed support groups for HIV-positive women as well as classes teaching these women how to avoid transmitting the virus to their children and partners.

'70s

Daniel Haller (MD '73) submitted an article to the *Journal of Clinical Oncology*, the biggest subspecialty journal in oncology, but never heard back from them—that is, until the paper was already published. To avoid conflicts of interest, Haller, who is editor in chief, was not allowed to know that his article about oxaliplatin (a chemotherapy used to kill colon cancer cells) had been accepted. He had worked with the drug's sponsor to obtain FDA approval for the drug. Haller is coprogram leader of the clinical oncology research program at the University of Pennsylvania Cancer Center and a professor of medicine at the University of Pennsylvania.

As a U.S. Navy officer in the 1980s, **Sarkis Chobanian** (MD '77) treated Supreme Court justices, members of Congress, and a U.S. president. A few years ago, Chobanian served his own term as president—of the American College of Gastroenterology. He is now in private practice in Knoxville, Tenn.

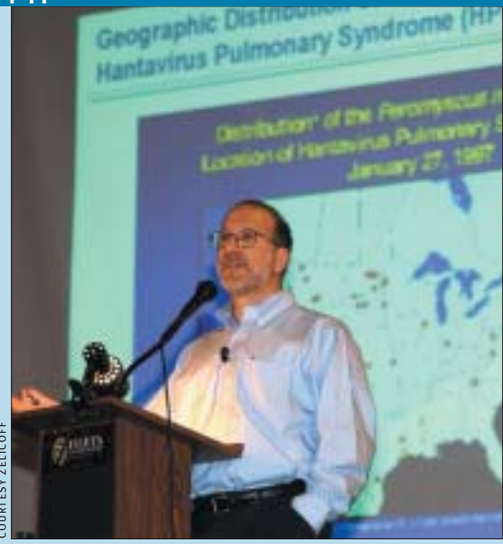
As a resident in radiology at the University of Colorado, **Calvin Neithamer Jr.** (MD '77) asked a patient to follow him from the commons area into the examining room. Every three steps severe pain in his legs caused the patient to stop. One day after undergoing a balloon angioplasty, the patient could walk with ease. From that moment on, Neithamer was hooked on vascular and interventional radiology. Today, in Inova Mount Vernon Hospital in Alexandria, Va., Neithamer is director of interventional radiology and regularly treats

ALAN ZELICOFF | BIO SLEUTH

BY JENNIFER MATSON

In May 2002, Alan Zelicoff (MD '79), an international intelligence analyst at Sandia National Laboratories in Albuquerque, N.M., received a file from Kazakhstan that had been hidden by the Soviet Union 31 years earlier. It documented a 1971 outbreak of smallpox that infected 10 people, killing three. Zelicoff was puzzled, because the Soviet Union had been a leading force in eradicating smallpox, and the last official case in the U.S.S.R. had occurred in 1936.

With a little detective work, Zelicoff succeeded in contacting the woman who'd first contracted the disease and interviewed her with the help



COURTESY ZELICOFF

A smallpox outbreak in the former Soviet Union prompted Zelicoff to sound an alarm 30-some years later.

patients with vein abnormalities and disorders of the uterus. He has led D.C.'s radiological society and is now president of the Chesapeake Interventional Radiology Society.

When **D. Lawrence Wickerham** (MD '76, General Surgery Resident '76–'77, Oncology Research Fellowship '81–'83) was a medical student at Pitt, he worked with Bernard Fisher at the National Surgical Adjuvant Breast and Bowel Project (NSABP) just a few years after Fisher released his famed study noting the effectiveness of lumpectomies versus radical mastectomies. Wickerham later returned to Pittsburgh and is now associate chair of the NSABP. These days he recruits participants for the STAR trial (a study of tamoxifen and raloxifene), which will include 19,000 women at high risk for breast cancer.

'80s

For two years, until he graduated from the program in 2002, **Richard Friedman** (MD '80) took two-hour flights from his home near Houston to attend MBA classes at the University of Chicago. He did this while serving as an associate professor of pediatrics in Baylor College of Medicine and chief of arrhythmia and pacing services at Texas Children's Hospital. Freidman put up with the commute because Chicago's program focused heavily on finance. Now, in addition to practicing medicine, he serves as the vice chair of pediatrics in charge of finance. Looking back to his days at Pitt, he's still thankful that Frances Drew, who was associate dean of student affairs when he applied, gave him an interview at the last minute.

'90s

Raymond Felgar (PhD '90, MD '92) helped develop the clinical flow cytometry and bone marrow laboratory at the University of Rochester. An assistant professor of pathology, Felgar compares his work on lymphoma and leukemia cells to looking at a bag of marbles. Perhaps 50 percent of the marbles (the "tumor cells") are marked with "dots" (certain proteins displayed on the cell surfaces). When identifying a cancer and setting a course for treatment, pathologists currently concentrate on the percentage of tumor cells that contain certain proteins—i.e., how many marbles have dots. Instead, Felgar wants to know how many dots are on each marble. He believes the amount of protein may reveal more about the cancer itself.

C. Y. Joseph Chang (Otology and Neurotology Fellow '94 –'95) listens—we mean really listens—to patients at the University of Texas Health Science Center at Houston and at the MD Anderson Cancer Center. Chang aims sound waves into the ear canals of chemotherapy patients at risk for hearing loss. In a healthy ear, return signals, or otoacoustic emissions, are produced, which Chang can detect through a microphone and amplifier. When hair cells are damaged—the cells are essential to hearing—no sound is produced. Chang hypothesizes that otoacoustic emissions tests can detect hearing loss in chemotherapy patients earlier than conventional hearing tests, and that they may lead to early treatment and prevention.

'00s

Deborah (Goldberg) Gilboa (MD '00) spent several years literally behind the scenes, culminating in her tenure as stage manager for Chicago's famed The Second City (the comedy troupe that nurtured comedians like Joan Rivers, Gilda Radner, and Bill Murray). She returned to Pittsburgh to attend medical school, thinking that she would prefer medicine to entertainment. In 2002, Gilboa won the American Academy of Family Physicians' Bristol-Myers Squibb Excellence in Graduate Medical Education Award—given to 20 family practice residents nationwide. Gilboa is now in a private practice in Kittanning, Pa.



1970 Hippocratean

A man in his 30s, complaining of a terrible stomachache, walked into the jungle hospital in Ecuador where **Larry Mathers** (MD '00) was working as a resident. Mathers ran a few tests, noting the man had a fever but otherwise was probably suffering from a cold or a flu. Hours later the man returned, begging to be admitted. Serial chest x rays revealed a fluid buildup between the membrane encasing the lung and the thoracic cavity. After an analysis of the fluid, Mathers determined the man had TB. Mathers says his experience with this strange case taught him that it is important for him to be flexible. Like Gilboa (see above), Mathers won the American Academy of Family Physicians' Bristol-Myers Squibb Excellence in Graduate Medical Education Award, making the University of Pittsburgh School of Medicine the only institution to have two of its alumni on the list for 2002. Mathers has moved to rural Tennessee to work in a family practice that recently won a federal grant to track the medical treatment of migrant workers who populate the region. *—MH, JM, & SZ*

p.s. Can you recognize the people in the yearbook photo above? Let us in on it at ***medmag@pitt.edu****.*



THE WAY WE ARE: CLASS OF '73

BY HEATHER McENTARFER

Some people will take a day off to play golf. **James McGreevy** (MD '73, Surgery Resident '73–'76 and '78–'81) flies an F-16 every Tuesday. McGreevy is a general surgeon and director of the residency program at the University of Utah. But he's also a lieutenant colonel in the U.S. Air Force Reserve—chief of Aerospace Medical Services for the 419th Fighter Wing. In 1991, he was on active duty as a flight surgeon during Desert Storm. He has since served in Tunisia, training physicians there in military medicine, and in Kuwait. Much of his downtime, if you can call it that, is spent on two wheels, bicycling 100–200 miles per week. He recently completed a 400-mile bike trek through Colorado.

McGreevy recalls his residency at Pitt as a formative experience, particularly because of faculty mentors such as Henry Bahnson, Mark Ravitch, and Ross Musgrave, all of whom he says taught important lessons about discipline,

of a translator. Zelicoff concluded that the woman, a scientist working on a fishing vessel, contracted smallpox through the air when her ship sailed 40 miles downwind of Vozrozhdeniye Island. Located in the Aral Sea between present-day Kazakhstan and Uzbekistan, Vozrozhdeniye was a Soviet biological warfare testing site during the Cold War.

Zelicoff presented his findings to the National Academy of Sciences in June 2002, sparking a heated debate among scientists and health officials: Should Americans be vaccinated against smallpox? Zelicoff warns that if—as evidence from the 1971 outbreak suggests—smallpox can be contracted through the air over long distances, a terrorist attack using the disease as a weapon could be devastating. However, there is also a one or two in one million chance that a person who receives the vaccine will die from it, according to the Centers for Disease Control and Prevention. Some scientists believe that Zelicoff's position is alarmist. His retort:

"If you believe that in the next 30 years there is at least a 1 percent chance that a terrorist will use smallpox to attack us, then the only rational strategy is to vaccinate everyone now."

patience, and caring.

McGreevy caught up with classmate **Peter Ferson** (MD '73, Surgery Resident '73–'78, Cardiac Resident '79–'80) during a camping trip to Utah in the early '90s. Ferson practices in Pittsburgh, as a professor of surgery within Pitt's Division of Thoracic Surgery, where his switch from cardiothoracic surgery to lung surgery in the late '80s made him UPMC's first surgeon to focus exclusively on the lungs. His camping trips have taken him across the western United States and Canada. Ferson combines traveling with a passion for photography. He loves the challenge of getting the perfect shot, like the time he tracked a mountain goat through the Canadian Rockies. And when his daughter's junior high held a summer contest (who could be photographed wearing the school T-shirt in the greatest places?), Ferson showed his competitive side: He captured her beside a buffalo in Yellowstone National Park and *above* the sign at Pikes Peak.

Ferson's got a silver eye, but **Charlotte Reed** (PhD '73) has golden ideas for those whose senses are impaired. Reed helps deaf people "hear" through some unusual channels—an arm, say, or a finger. After earning her doctorate in Pitt's bioacoustics program, Reed earned a postdoctoral fellowship at MIT and has conducted research there ever since. Whether by placing one's hand on a speaker's face or signing into another's hand, people who are deaf and deaf-blind have long communicated through touch. Reed studies tactual communication as a member of MIT's Sensory Communication Group and works to create high-tech aids that transfer sound into patterns of vibration that can be "heard" through the skin. She has evaluated several aids on the market, helping people with profound deafness and deaf-blindness.



The Class of '73 and their guests gathered at the Duquesne Club during graduation weekend. FROM LEFT: R. Bragdon, J. Smith, B. Bragdon, G. Smith, J. Trompeter, R. Lewis, C. Lewis, T. Trompeter, J. Fusco, G. Rudenstein, R. Fusco, R. Rudenstein, L. Weber, R. Landay, E. Mandel (Weber), F. Landay, D. Kobaly, M. Kobaly

PETER SAFAR
APRIL 12, 1924–AUGUST 3, 2003



HIPPOCRATEAN

Safar, 1970

When Peter Safar was diagnosed with advanced cancer at age 78 last year, he neither reduced his workload nor took a vacation. "Even as recently as January," says his wife, Eva Safar, "he was often in pain, but he was determined to put in one more grant application."

Safar's accomplishments already seemed like the work of three men. He established the first ICU as we know it. At Pitt, he founded the anesthesiology department in the school and the world's first critical care medicine program training physicians in intensive care. Safar was called "the father of CPR" for documenting and advocating the lifesaving techniques now familiar to millions. Resusci Anne, the first CPR training mannequin, was developed at Safar's behest. In the 1960s, he designed one of the first modern ambulance services, providing Pittsburgh's Hill District with an unprecedented quality of emergency care. Safar was nominated for the Nobel Prize three times.

His recent work focused on using rapid deep chilling to create a sort of suspended animation in trauma victims. Experiments suggest that brain damage can be reduced or eliminated, even when victims are resuscitated after one or two hours. Safar hoped that CPR would thus evolve into CPCR—Cardiopulmonary Cerebral Resuscitation.

Despite the energy he devoted to work, Safar cultivated a love of music. He played classical music on a baby grand piano that had belonged to his family in Vienna. He and his wife stopped entering the Pittsburgh Symphony Orchestra's waltzing contest after winning it three consecutive years. What kind of dancer was he? "Outstanding," says Eva Safar. "I met my husband when I was 17, and nobody else ever quite measured up." —*CS*

IN MEMORIAM

'30s

HAROLD SAMUEL AGNEW (MD '37)
AUGUST 7, 2003

REGIS A. WOLFF (MD '38)
AUGUST 27, 2003

LAWRENCE C. BUVINGER (MD '39)
JUNE 18, 2003

'40s

RALPH G. LEIGHTY (MD '42)
JULY 1, 2003

JOHN B. MARTIN (MD '43A)
JULY 22, 2003

ARNOLD SAMPSON (MD '44)
JUNE 15, 2003

'60s

JAMES THEODORE (MD '62)
AUGUST 17, 2003

FACULTY

JESSICA LEWIS
AUGUST 21, 2003

ELMER HOLZINGER: THE MASTER

BY MEGHAN HOLOHAN



COURTESY HOLZINGER

Holzinger

As Tara Cronin walked to practical exam, held at the beginning of her third year, someone handed her a piece of paper. The paper explained that she was to give the "patient" (an actor) a full heart examination without inquiring about his history. Walking into the room, she saw a man in his 20s sitting on a long table. She felt confident, until she saw Elmer Holzinger (MD '54) sitting in the corner.

Holzinger is tall and lanky. He often wears a bow tie and his demeanor recalls the late Fred Rogers. He has a soft, soothing voice and is patient. He wouldn't inspire fear in many, but Cronin knew better. Holzinger's reputation as a master in the art of the physical examination preceded him.

Cronin approached the patient and put on her stethoscope. She listened to his heart while he sat upright. She listened to his heart as he lay down. Front, back, up, down. She thought she'd covered it all. Holzinger watched quietly throughout. When Cronin was finished, he explained that she forgot to roll the patient onto his side to listen to his heart. In this position, the heart is closer to the surface, making possible "gallops" louder.

Holzinger has been teaching Pitt medical students for 30 years, and is one of the School of Medicine's most beloved and respected clinical professors. The hundreds, possibly thousands, of students who've trained on a rotation with him aren't the only ones to recognize his prowess as a teacher. In 1997, the American College of Physicians named Holzinger a Master—an honor that is just as prominently displayed on his wall as the Humanitarian Award that med students bestowed upon him in 2000. He was the inaugural winner of that award, which recognizes the teacher or physician who shows the most compassion toward patients.

On a recent afternoon, Cronin, now in her fourth year of medical school, again reviews a physical examination with Holzinger. This time, however, it's a real patient—one of Holzinger's. This is Cronin's second rotation with him since that day last year when he observed and critiqued her performance on the heart exam. Having quickly gotten over her initial intimidation, she asked to be placed with him specifically because she wanted to learn from a master how to perform a thorough exam.

What has she learned from Holzinger so far? He never orders tests unless he cannot make a diagnosis based on the empirical evidence he collects. And he is not just thorough, he is fervent in his questioning. He doesn't stop with how many drinks a patient consumes in a week. He wants to know what else is going on. *How is the family? How is work?*

Cronin shares with Holzinger the results of the history and exam she just completed. She rattles off a list of symptoms—the man has pain in his back, underneath his shoulder; it gets worse when he lies down. What does she think it is, Holzinger wants to know. She is quick with an answer—*a perforated ulcer?*—maybe too quick. As he starts to question why she has come to this conclusion, she hesitantly suggests it could be pancreatitis instead. He concurs. (It was.)

Holzinger left private practice in the '60s to teach at St. Francis Hospital. He chaired the Department of Medicine and headed the residency program at St. Francis from 1970 to 1999. He has no plans to retire, which is good news for students like Cronin. He builds time into his schedule for teaching. Oftentimes he'll stay in the office until midnight to accommodate students. As he sits in his office talking about his love for teaching, another student interrupts. She needs his assistance. He politely excuses himself, bounding down the hall to listen to her patient evaluation. ■

MEDICAL ALUMNI ASSOCIATION OFFICERS

FREDDIE H. FU (MD '77)
President

STANLEY M. MARKS (MD '73)
President-elect

JOHN F. DELANEY (MD '64)
Vice President

GRAHAM JOHNSTONE (MD '70)
Secretary

PETER FERSON (MD '73)
Treasurer

ROBERT E. LEE (MD '56)
Historian

CHARLES M. HEFFLIN (MD '74)

JAMES JOHNSTON (MD '79)

JOHN KOKALES (MD '73)

JOANN VIRGINIA NARDUZZI (MD '62)
Members at Large

SUSAN DUNMIRE (MD '85)
Interim Director

M-200K Scaife Hall
University of Pittsburgh
Pittsburgh, PA 15261
tel 412-648-9090; fax 412-648-9500
medalum@medschool.pitt.edu



They administered dopamine drips and CPR while zipping down Centre Avenue. They interpreted EKGs on the fly in the back of a modified Ford Econoline. Doctors had never seen patients come into the ER like that. By 1975, the Freedom House Ambulance Service, the brainchild of Pitt's Peter Safar and The Maurice Falk Medical Fund's Phillip Hallen, was a model for the nation, and folks in Pittsburgh's Hill District learned to tell the emergency dispatcher, "Now don't you send us the police. You send us those Freedom Boys." Watch for an in-depth look at Freedom House in a future issue. (And let us know if you can identify these fellows.)

PHOTO | 1970 *HIPPOCRATEAN*

CALENDAR

OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

SCHOOL OF MEDICINE AAMC RECEPTION

NOVEMBER 9
114th Annual Meeting of the Association of American Medical Colleges
Hilton Washington and Towers, 6 p.m.
Washington, D.C.
For information:
Kristin Lang
412-648-9000
kristin@medschool.pitt.edu

CLASS OF '59 REUNION

MARCH 13–19
Lago Mar Resort and Club
Fort Lauderdale, Fla.
For information:
Richard Finder, MD '59
954-925-7461
rfinder320@aol.com

INAUGURAL MINORITY ALUMNI WEEKEND

APRIL 16–18
Pittsburgh
For information:
Office of Minority Affairs
412-648-8987
minorityaffairs@medschool.pitt.edu
or
Medical Alumni Association
412-648-9090 or 1-877-MED-ALUM
medalum@medschool.pitt.edu

PITT MED GOLF OUTING

APRIL 24
Quicksilver Golf Club
Midway, Pa.
8:30 a.m.
For information:
Ronald Trible
412-648-9090
rptst7@pitt.edu

MEDICAL ALUMNI WEEKEND 2004

MAY 21–23
Classes celebrating:

1939	1969
1944	1974
1949	1979
1954	1984
1959	1989
1964	1994

For information:
Medical Alumni Association
412-648-9090 or 1-877-MED-ALUM
medalum@medschool.pitt.edu

SENIOR CLASS LUNCHEON

MAY 21
Pittsburgh
For information:
Medical Alumni Association
412-648-9090 or 1-877-MED-ALUM
medalum@medschool.pitt.edu

TO FIND OUT WHAT ELSE IS HAPPENING AT THE MEDICAL SCHOOL, GO TO www.health.pitt.edu



GETTY

UNTOLD RICHES

What has more class than a typical Pitt med reunion? The first ever Minority Reunion Weekend, which will link med school alumni from as many as 39 classes between 1948 and 2003. With hundreds of invitees, it promises to not only entertain, but to celebrate one of the strengths of the school. Perhaps the gathering will even begin a tradition that will help light the way to Pitt for the nation's top minority recruits.

Minority Reunion Weekend
April 16–18
For more information:
Medical Alumni Association
412-648-9090
medalum@medschool.pitt.edu or
minorityaffairs@medschool.pitt.edu

UNIVERSITY OF PITTSBURGH
SCHOOL OF MEDICINE
SUITE 401 SCAIFE HALL
PITTSBURGH, PA 15261

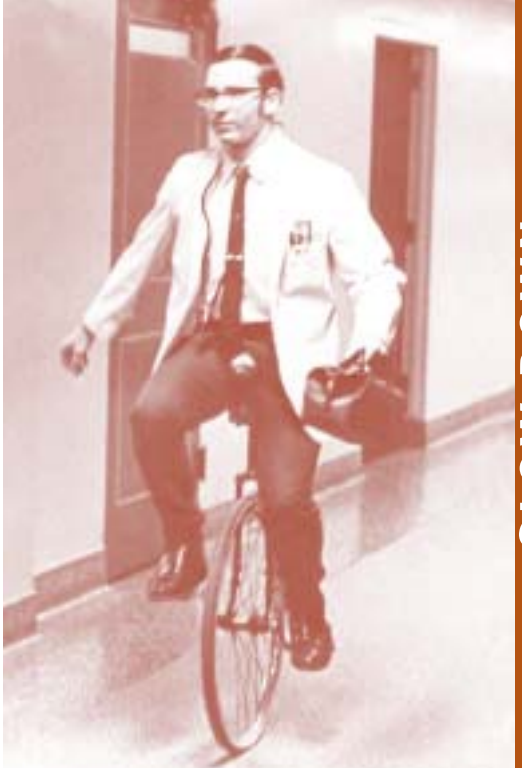
CHANGE SERVICE REQUESTED

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO 1752 PITTSBURGH, PA

POSTAGE WILL BE PAID BY ADDRESSEE

SCHOOL OF MEDICINE
MEDICAL ALUMNI ASSOCIATION
UNIVERSITY OF PITTSBURGH
4200 5TH AVE
PITTSBURGH PA 15213-9910



SLOW DOWN

LET US CATCH UP

TELL US YOUR NEWS: CAREER ADVANCEMENTS, HONORS YOU'VE RECEIVED, APPOINTMENTS, VOLUNTEER WORK, PUBLICATIONS . . . AND WE LOVE TO HEAR OLD PITT MEMORIES.

NAME _____

DEGREE/PROGRAM/YEAR _____

ADDRESS _____

CITY, STATE, ZIP _____

HOME TELEPHONE _____

BUSINESS TELEPHONE _____

E-MAIL _____

PLEASE PUBLISH MY E-MAIL ADDRESS. YES ☐ NO ☐

NEWS _____

TO GET US YOUR NEWS, DROP THIS IN THE MAIL. YOU MAY ALSO FAX: 412-648-1813 OR E-MAIL: medmag@pitt.edu